IMPROVING THE DIAGNOSTIC PATHWAY OF SARCOMA PATIENTS

EXPERIENCES, OUTCOMES, AND FUTURE PERSPECTIVES

VICKY SOOMERS

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Experiences, outcomes, and future perspectives

Vicky Soomers

The research presented in this thesis was performed at the department of Medical Oncology of the Radboud University Medical Center and carried out within the Radboud Institute of Health Sciences.

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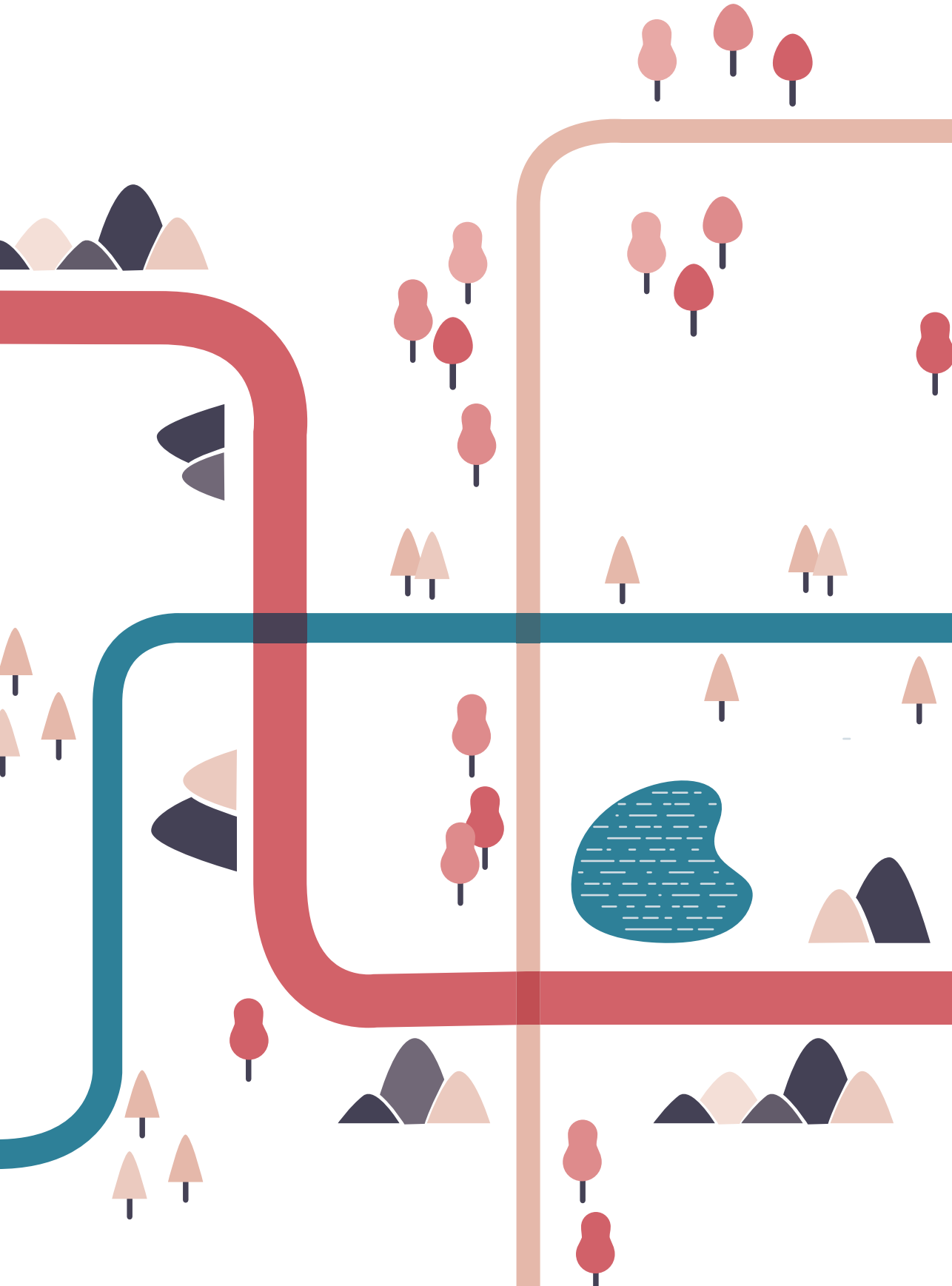
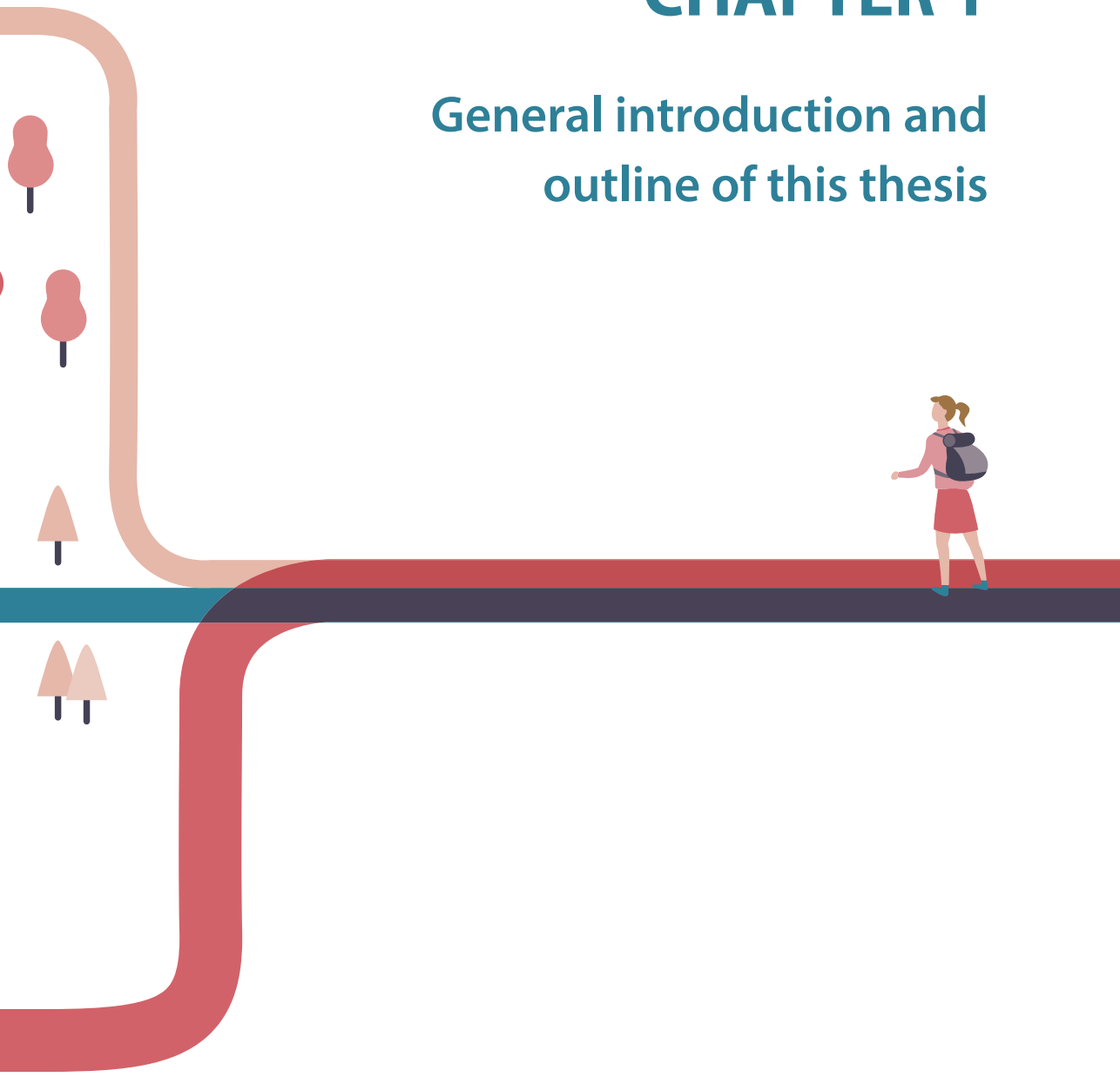


CHAPTER 1

General introduction and outline of this thesis



Sarcomas

Sarcomas are a group of solid malignant tumours of mesenchymal origin. They comprise more than 70 histological subtypes[1]; approximately 80% of sarcomas originate in soft tissue, the remainder in bone. They have considerable heterogeneity with respect to age of onset, anatomic location, speed of progression, and outcome (Figure 1). Together, they are a typical example of rare cancers (incidence <6 per 100,000 per year), accounting for approximately 1-2% of all malignant neoplasms in adults, with an estimated incidence of 4-5 per 100.000 per year[2, 3]. However, the incidence of several subtypes is even below 1 per 100,000/year.

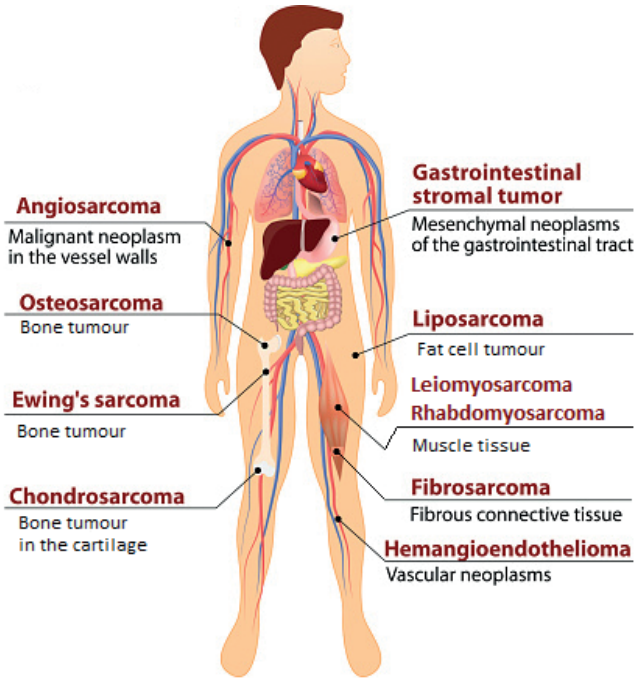


Figure 1: sarcoma subtypes
Adapted from www.news-medical.net

For localised disease, surgery is the standard treatment of all patients with STS[4]. The typical wide excision is preceded or followed by radiotherapy in case of high grade, deep, or >5cm lesions. Hyperthermic limb perfusion may be an option prior to limb-preserving surgery. (Neo-)adjuvant chemotherapy is not standard in adult-type STS but could be discussed with patients in case of either marginally resectable tumours or in patients with tumours at high-risk of developing distant metastases.

Treatment of BS differs per subtype. These subtypes have distinct patterns of incidence. The most common subtypes are osteosarcoma, Ewing sarcoma, and chondrosarcoma[5]. Osteosarcoma and Ewing sarcoma have a higher incidence among adolescents, whereas chondrosarcomas are more common in older age[3].

Conventional osteosarcomas are always high-grade and metastasise frequently. They are curatively treated with extensive (neo-)adjuvant combination chemotherapy in addition to surgery[6]. Patients with metastases at diagnosis are treated with curative intent following the same principles, but responses are less durable and patients have a worse prognosis.

Ewing sarcomas are high-grade tumours, treated with neo-adjuvant combination chemotherapy, followed by local therapy (preferably surgery), and adjuvant chemotherapy[6]. Radiotherapy should be considered in cases of inadequate surgical margins or poor histological response to neo-adjuvant chemotherapy. Primary radiotherapy is applied as local therapy in case of unresectable tumour locations. Patients with primary metastases are treated with the same approach. Whole-lung irradiation can be considered in patients with lung metastases, the role of local therapy for other metastases is unclear. There is no clear benefit from high dose chemotherapy followed autologous stem-cell rescue compared to standard chemotherapy with whole-lung irradiation in patients with pulmonary or pleural metastases[7].

Most chondrosarcomas are low-grade and can be treated with surgery or radiotherapy[6]. High-grade chondrosarcomas should be excised with wide margins, if this cannot be achieved with limb salvage, amputation should be considered. Several less common subtypes, such as mesenchymal chondrosarcoma, may be more chemotherapy sensitive.

For most patients with secondary metastatic disease, regardless of subtype, curative therapy is no longer possible. In general, standard therapy for metastatic STS and BS is chemotherapy[4, 6], but in selected cases of oligometastatic disease, local therapy such as surgery, radiotherapy or radiofrequency ablation, of metastases can be considered. The feasibility and benefit of such treatment depends on the number and site of metastases, the interval since primary diagnosis, and complaints caused by the tumour.

Survival rates of patients with sarcomas vary widely. In the Netherlands, 5-year survival rates were 60% for high-grade BS, 93% for low-grade BS, 46% for high-grade STS, and 81% for low-grade STS between 2017-2018[8]. There is a large variability across histological subtypes: in an American database consisting of 78527 patients with sarcoma, the lowest 5-year cause specific survival, all grades combined, for STS was found in angiosarcoma

(53.8%), and the highest in dermatofibrosarcoma (99.2%)[5]. For BS, 5-year cause specific survival was lowest in Ewing sarcoma (64%), and highest in chondrosarcoma (81.9%)[5].

Despite efforts to improve survival outcomes of sarcoma patients with novel imaging and treatment strategies, only limited progress has been made. Another approach to improve outcomes is to improve the diagnostic pathway. Due to the rarity of the disease and the heterogenous presentation, the diagnostic pathway may be difficult and prolonged, resulting in higher disease stage at diagnosis. This is a common problem among rare cancers and unfortunately, sarcoma patients are no exception: 7% of BS and 14% of STS patients have metastases at diagnoses, with a large variance among subtypes, e.g. 42% of Ewing sarcomas are metastasized at diagnoses[8]. This thesis focusses on the diagnostic pathway of sarcoma patients and tries to identify its effect on outcomes and ways for improvement.

Diagnosing sarcoma

Previous research has shown that the sarcoma diagnostic pathway is variable and long in a high proportion of patients[9]. Its length varies from several weeks to several years, and patients can follow different referral routes to diagnosis.

To understand the diagnostic pathway, it is important to use a standardized framework with clear definitions. In this thesis, we will use the model first described by Olesen et al[10, 11], which we have adapted to fit the sarcoma diagnostic pathway, as shown in Figure 2. The time from first symptom until histological diagnosis, is defined as the total interval. This is further divided into a patient and diagnostic interval. The diagnostic interval encompasses the primary care, secondary care, and tertiary care interval. A long total interval may be caused by several factors. First, diagnosis may be delayed due to a prolonged time to presentation by the patient, a time interval known as the patient interval. Second, referral by general practitioner to secondary or tertiary care may take long due to unfamiliarity with sarcomas and heterogeneity of its symptoms. This time interval is known as the primary care interval. Third, the final diagnosis may be delayed due to low awareness among non-sarcoma specialists, delays for imaging, biopsy, and biopsy reporting, leading to late referral to a sarcoma centre from the secondary care hospital. This interval, the secondary care interval, encompasses the time from referral by the GP until referral from a secondary care specialist to a sarcoma centre. Fourth, the tertiary care interval, the time from referral to a sarcoma centre until definitive (pathological) diagnosis, can be long because histological diagnosis can be complex, and histology often needs to be reviewed in an expert panel or additional molecular investigations need to be done, dependent on the trajectory within the secondary care interval.

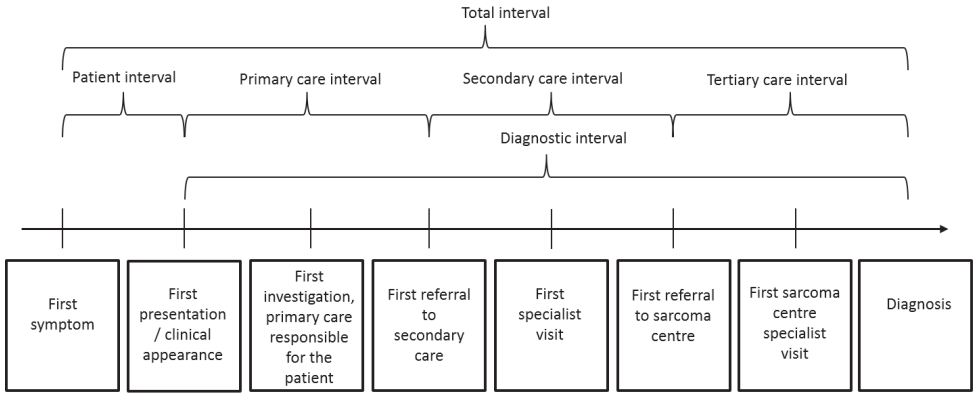


Figure 2: time intervals in the route from first symptom until diagnosis[9]

Factors contributing to the total interval length

Several factors are thought to influence the total interval length. These can be divided into patient factors (e.g. socio-demographic characteristics and co-morbidities), tumour factors (e.g. histology and location), and healthcare system factors (e.g. access and referral pathways).

These factors can be different for different sarcoma histologies and age groups. Until now, published literature has been mainly retrospective and among small groups of patients, generating contradicting results[9]. For sarcoma, it is especially interesting to study different age groups as it accounts for about 10% of all invasive cancers among adolescents and young adults (AYAs), and only 1-2% of all malignancies among adults[12]. Although survival for AYA cancers have paralleled those of childhood cancers since the year 2000[13], this improvement is less distinct for sarcomas[14]. The distribution of different histologic sarcoma subtypes is linked to age; several "paediatric sarcomas" have a (second) peak during adolescence, such as rhabdomyosarcomas, Ewing sarcomas and osteosarcomas[15]. Synovial sarcomas have a peak incidence in patients aged 30-35. The different biological and clinical behaviour of these sarcomas, along with age-specific characteristics of AYA patients, such as developmental, physical, psychosocial and economic issues (e.g. becoming financially independent, infertility issues, care for small children), may contribute to different diagnostic pathways of this group as compared to older adults. Although the diagnostic pathway and its contributing factors have been studied among children, and teenagers and adolescents (aged 15-25), it has not been described in detail for patients aged 25-39[16-20].

Healthcare system factors have been difficult to study, as there is a lack of studies comparing different healthcare systems. In order to improve outcomes, many countries have introduced some form of centralization of diagnosis and treatment for patients with sarcoma. Patients diagnosed at sarcoma centres and discussed in multidisciplinary teams, receive the correct diagnosis and treatment more often than those diagnosed elsewhere[21]. In a study among 1463 French and Italian patients diagnosed with sarcoma, more than 40% of histological diagnoses were modified by the expert pathologist[21]. The major discrepancies were related to histological grade, type, and subtype. A second study, including 12528 STS patients compared those who were presented in a multidisciplinary meeting before and after initiation of treatment[22]. The former group had worse prognostic characteristics, but there was a better compliance to clinical guidelines, resulting in better relapse-free survival than those who were presented in the multidisciplinary team after treatment initiation. The same study group has shown that sarcoma patients receiving their surgical treatment in a sarcoma centre, have better overall survival than those operated on in non-reference centres[23].

Until now, there is no published data in which diagnostic pathways of two or more healthcare systems have been directly compared. It would be ideal to study comparable healthcare systems with differences in organization of sarcoma care. This would contribute to identification of healthcare system factors influencing total interval length specifically for sarcoma care, as well as identify cultural and geographical factors which may influence total interval length.

Effect of total interval length on outcomes for sarcoma patients

The cumulative effect of events leading to delays in each interval component, may jeopardize outcome and prognosis[24]. In several cancers there is an association between shorter times to diagnosis and more favourable outcomes, such as breast- , colorectal-, head and neck-, testicular cancer, and melanoma[25]. In sarcomas, the most investigated effect of a long total interval is that of increased size of the lesion, leading to a lower chance of uncomplicated complete resection, greater risk of amputation, and potential for developing metastases[26]. Data on the effect of the total interval on survival in sarcoma is lacking.

Traditionally, clinicians have been interested in clinical outcomes. Patient-reported outcomes (PROs) are other important and powerful tools to inform clinicians, as well as patients themselves and policy-makers. PROs are reports of the status of a patient's health condition, directly reported by the patient. Several patient-reported outcome measures (PROMs) exist; these are questionnaires patients complete on their health. Health-related quality of life (HRQoL) is such a measure and encompasses the patient's

subjective experience of his health status, encompassing physical, psychological, and social functioning[27]. Integration of PROMs in standard care has been shown to improve short-term outcomes and overall survival among patients with metastatic cancer[28]. Only few studies have investigated the association between total interval length and patient-reported outcomes. In lung and colorectal cancer no association was found, among endometrial and ovarian cancer patients a shorter time to diagnosis lead to better HRQoL and patient satisfaction[25]. To our knowledge, there is no published data about the effect of total interval length on HRQoL of sarcoma patients. Furthermore, which cut-off point for interval length should be applied in terms of effect on clinical outcomes, such as survival, and patient-reported outcomes, such as HRQoL, is unknown. Moreover, whether there will be a clear and similar cut-off for both outcomes, survival and HRQoL, in sarcomas is uncertain.

Apart from studying the effect of total interval length on outcomes during treatment and shortly thereafter, it is important to study long-term effects of total interval length. With a growing incidence of sarcoma, the number of sarcoma survivors increases. Currently, there are an estimated 280,000 sarcoma survivors in Europe[3]. Survivorship focusses on the health and well-being of a person with cancer from the time of diagnosis, until the end of life[29]. It includes issues related to follow-up care (including regular health and wellness check-ups), late effects of treatment, cancer recurrence, second cancers, and quality of life. For sarcoma survivors, the diversity of clinical presentations, variation in treatments, demographic and other factors, makes it difficult to describe survivorship issues that are applicable to all sarcoma survivors. There is a lack of studies looking at long-term effects, such as its influence on HRQoL, of a long total interval among adult sarcoma survivors.

Outline of this thesis

The aim of this thesis is to gain insight in diagnostic pathways of adult sarcoma patients, to identify risk groups for prolonged diagnostic pathways, and investigate the impact of the diagnostic pathway with respect to clinical and patient-reported outcomes for diagnostic pathway length. In this thesis we will discuss data from Dutch and English patients. Approximately 1200 and 5000 people are diagnosed with sarcoma each year in The Netherlands and England, respectively[30, 31]. In both countries, general practitioners (GP) have an important role as healthcare gatekeepers. Their healthcare sector is largely funded by the government from general taxation, and a smaller amount from insurance contributions and fees paid by its user. However, most services, such as GP care, are free at the point of use. In general, people consult their GP who then decides whether referral is needed and determines the acuteness and location of the referral. In the UK, privately insured patients can also self-refer to a hospital without seeing a GP. In both countries, patients suspected of sarcoma are usually referred by their general practitioner for further analysis to a hospital, where a medical specialist refers onwards to a sarcoma centre in case of an actual sarcoma. In the Netherlands, this is formally organized for patients with bone sarcoma, for patients with soft tissue sarcoma this is recommended, but not mandatory. In the United Kingdom, care for all sarcoma patients has formally been centralized. These comparable healthcare systems with differences in organization of sarcoma care are thus a good fit to compare diagnostic pathways.

We started by conducting a systematic review, which is described in **chapter 2.** It gives an overview of what was already known about the total interval of sarcoma patients by quantifying its length, identifying contributing factors, and determining the impact on patients' outcome in terms of clinical and patient-reported outcome.

In order to study the diagnostic pathway in more detail and identify bottlenecks as viewed by patients, we conducted interviews among Dutch and English patients with sarcoma. This qualitative study, described in **Chapter 3**, illustrates the diagnostic pathway as experienced by sarcoma patients, and its impact on HRQoL and care satisfaction.

The results of the review and qualitative study were a prelude to three studies described in this thesis. First, we conducted a cross-sectional cohort study among a Dutch sarcoma survivorship population, known as the SURVSARC study. Second, we studied the diagnostic pathway of English young adults aged 25-39, to identify factors associated with a prolonged pathway. Third, we describe the design of a longitudinal, prospective, international study, known as the QUEST study.

Chapter 4 and **chapter 5** describe results of the SURVSARC study. For this cross-sectional study, patients diagnosed with sarcoma 2-10 years ago in one of six Dutch participating sarcoma centres were asked to complete a questionnaire on diagnostic pathway, treatment, and outcome measures such as HRQoL. In **chapter 4** we report interval lengths of sarcoma survivors and identify factors associated with prolonged intervals. The effect of these interval lengths on current HRQoL of sarcoma survivors is described in **chapter 5.** We also examine the impact of diagnostic pathway length on patients' subjective feeling of its impact on HRQoL, and study to what extent this subjective feeling is of influence on HRQoL. Lastly, we describe the results of a qualitative analysis of why some patients perceive a negative influence of diagnostic pathway length on their HRQoL.

In **chapter 6** we describe the results of English young adults diagnosed with cancer in the past five years, who were treated at one of the six participating Trusts. Since the incidence of sarcoma is relatively high among AYAs, and care for these patients is challenged by age-specific needs, comparing sarcoma patients with other cancer AYA patients may be contributing to gaining insight in the sarcoma-specific diagnostic pathway for this age group. Apart from a quantitative analysis of the diagnostic pathway, in this chapter we present suggestions to improve the diagnostic pathway for young adults made by the study population. These open field answers were qualitatively analysed and the results are presented in chapter 6.

The third study is the QUEST study (QUality of life and Experiences of Sarcoma Trajectories). In **chapter** 7 we describe its design. It is a longitudinal, prospective, international study we developed and has recruited patients from 2018-2020. Participants with a new diagnosis of sarcoma, treated in one of five sarcoma centres in the Netherlands or three centres in England, were asked to complete questionnaires at time of diagnosis and during a follow-up period of two years. The study aims to quantify total interval, identify factors associated with interval length, and determine the association between total interval and HRQoL, stage and tumour size at diagnosis, progression-free survival, and overall survival. We hope this will lead to the identification of risk groups and points of action to optimize their total interval. Furthermore, identifying a clinically relevant cut-off point for short and long intervals, which could differ between subtypes, will guide policy makers, healthcare providers, and patients to improve referral pathways.

Chapter 8 provides a summary of the results and discusses the practical implications of the findings in this thesis and future research perspectives.

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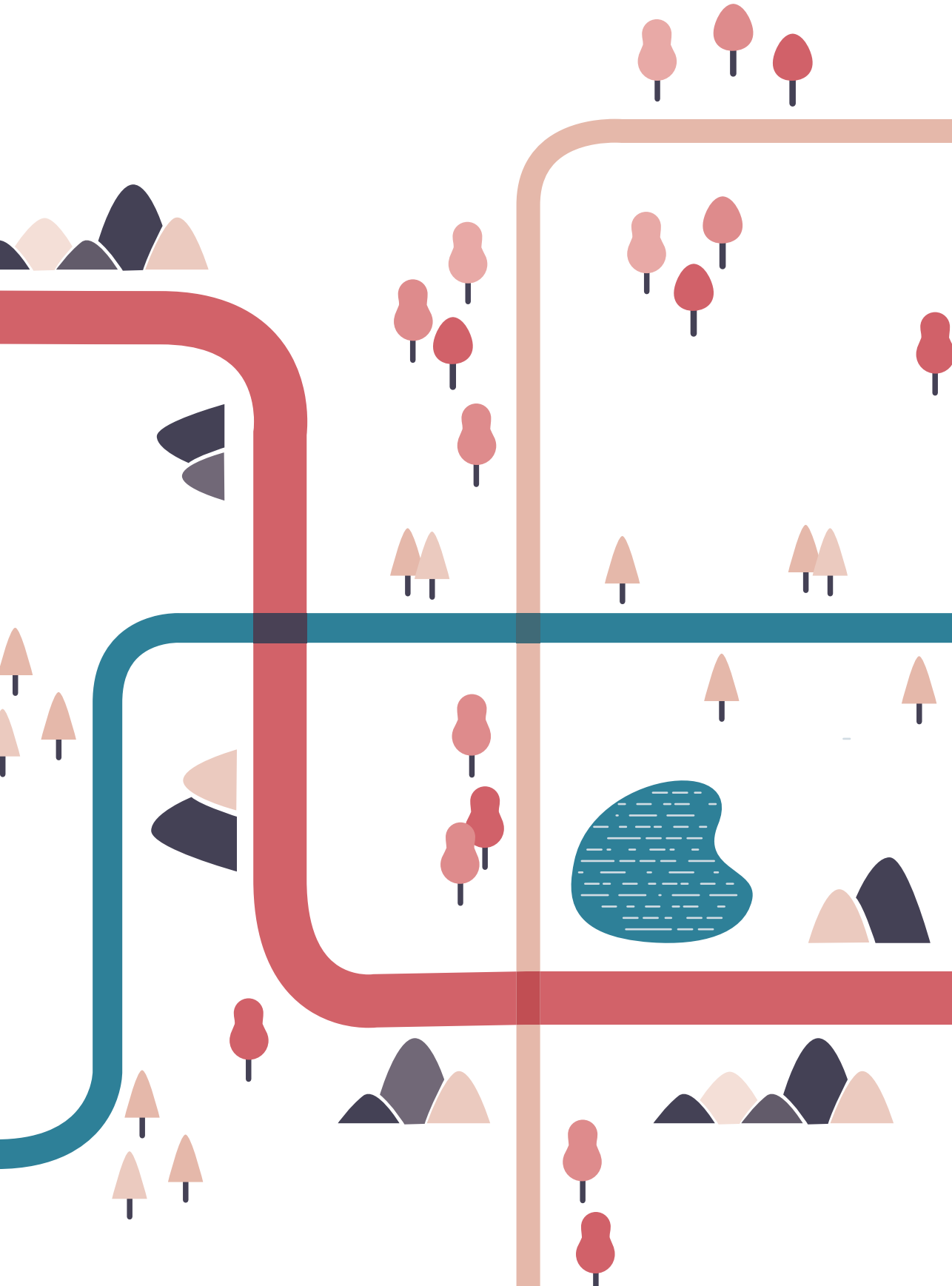
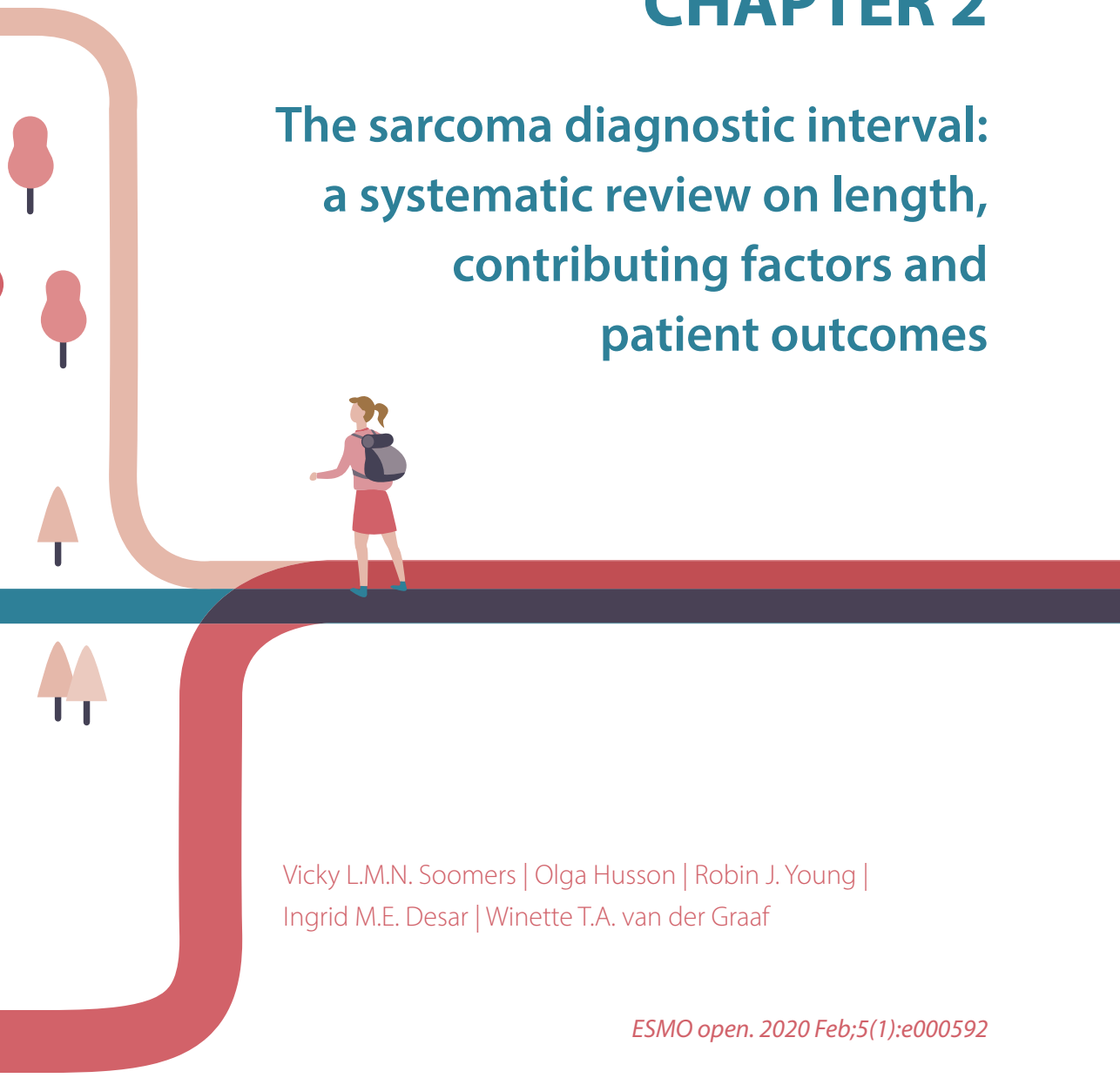


CHAPTER 2

The sarcoma diagnostic interval: a systematic review on length, contributing factors and patient outcomes



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Abstract

Background

Sarcomas are rare and heterogeneous mesenchymal tumours of soft tissue or bone, making them prone to late diagnosis. In other malignancies, early diagnosis has an impact on stage of disease, complexity of therapeutic procedures, survival and health-related quality of life (HRQoL). Little is known about what length of diagnostic interval should be considered as delay in patients with bone (BS) or soft tissue sarcomas (STS).

Objectives

To quantify total interval(defined as time from first symptom to histologic diagnosis) and its components, identify contributing factors to its length and determine the impact on patients' outcome in terms of mortality and HRQoL.

Methods

A systematic review was conducted according to PRISMA guidelines.

Results

Seventy-six articles out of 2,310 met the predefined inclusion criteria. Total intervals, varied broadly; 9-120.4 weeks for BS and 4.3-614.9 weeks for STS. Older age and no initial radiologic examinations were contributing factors for a long interval in BS, while in STS results were conflicting. The impact of length of total interval on clinical outcomes in terms of survival and morbidity remains ambiguous; no clear relation could be identified for both BS and STS. No study examined the impact on HRQoL.

Conclusion

The length of total interval is variable in BS as well as STS. Its effect on outcomes is contradictory. There is no definition of a clinically relevant cut-off point that discriminates between a short or long total interval

Introduction

Sarcomas are a rare group of solid malignant mesenchymal tumours, which comprise more than 70 histological subtypes. They have considerable heterogeneity with respect to age of onset, anatomic location, tempo of progression and outcome. Approximately 80% of sarcomas originate in soft tissue, the remainder in bone. Sarcomas form a typical example of rare cancers, with an estimated European incidence averaging 4-5 per 100 000 per year[1]. Patients with rare cancers have a higher mortality rate than those with common cancers because of delays to accurate diagnosis and subsequent suboptimal or inadequate treatment, fewer developments in novel therapies and reduced opportunities to participate in clinical trials[2].

Early and accurate diagnosis of cancer is important to optimise patient outcomes in terms of local disease control, overall survival and health-related quality of life (HRQoL)[3, 4]. The absence of a typical and uniform sarcoma presentation, the lack of public awareness, and the limited experience of primary and secondary healthcare professionals with sarcomas can result in a prolonged total interval and late referral to specialist sarcoma centres. The total interval is the time between first symptoms and (preferably histological) diagnosis(Figure 1)[5]. To date, the impact of late referrals on sarcoma patient outcomes has been understudied and reports have been contradictory.

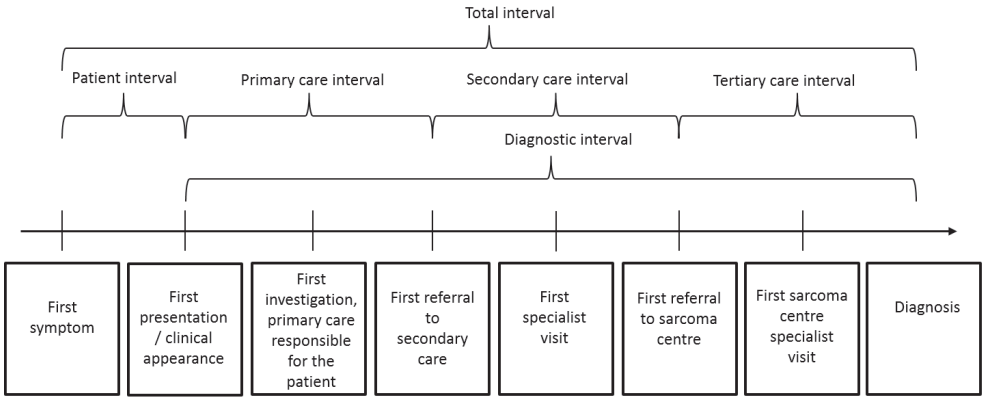

Figure 1: time intervals in the route from first symptom until diagnosis

Adapted from Olesen et al, 2009.
-Total interval: from first symptom to diagnosis;
-Patient interval: from the date the patient first noticed a sarcoma related symptom until the first presentation to a doctor with this symptom;
-Diagnostic interval: from first presentation to a doctor until diagnosis;
-Primary care interval: from first presentation to a general practitioner (GP) until first referral to secondary care (if applicable) or to a specialist sarcoma centre;
-Secondary care interval: from referral to secondary care until referral to tertiary care (a specialist sarcoma centre);
-Tertiary care interval: from referral to a specialist sarcoma centre until the date of (histological) diagnosis.

To inform interventions that shorten the total interval, better insights are needed into the determinants of each component of the total interval, such as socio-demographic, clinical, psychological and healthcare factors. The aim of this systematic review is to examine the total interval of sarcoma patients by quantifying its length, identifying contributing factors, and determine the impact on patients' outcome in terms of mortality and HRQoL. .

Material and methods

Search strategy

We conducted a systematic review according to PRISMA guidelines[6]. The review is registered in PROSPERO under registration number CRD42017062492.

A computerized search of the literature through Pubmed (1946-present), MEDLINE (1950-present), EMBASE (1974-present), Web of Science (1945-present) and Cochrane Library was carried out with the help of a librarian of the Radboudumc by two researchers (VS and OH) on February 28th 2019. The search strategy combined terms related to "sarcoma", "delayed diagnosis", "early diagnosis" or "referral". The search string is presented in supplementary material A.

Selection criteria

Studies were included if they met the following criteria: (1) study participants had a proven diagnosis of sarcoma; (2) the total interval or any of its components as defined in Figure 1 were available; (3) the full-text paper was available in English. Reviews were excluded because they did not contain original data and single case reports were excluded to limit selection bias.

Definition

The following definition was used: the total interval, defined as time between first symptoms and (histological) diagnosis, which includes both a patient and diagnostic interval; the latter can be further divided into a primary, secondary and tertiary care interval. The intervals and their associated time points are illustrated in Figure 1. This figure was adapted from Olesen et al[5, 7] by adding a tertiary interval , consistent with centralised sarcoma care pathways.

Data extraction and synthesis

Study design, inclusion period, study population, length of total interval and its components, and effect of total interval on outcomes, such as metastases at diagnosis, overall survival and HRQoL, were extracted from included articles. Factors influencing length of total interval or its components were extracted and organized as tumour

specific factors (e.g. histology), patient specific (e.g. age) or healthcare related (e.g. available imaging studies). Based on our clinical experience, previous reports and different healthcare providers treating these groups of patients, we expected to find different results for bone sarcoma (BS) and soft tissue sarcoma (STS) , and data was thus presented in separate tables. Due to the heterogeneity of inclusion criteria and methods, it was not possible to conduct a meta-analysis, so results were reported descriptively.

Results

Included articles

Our search yielded 2304 unique hits. The reference lists of relevant articles were searched for additional studies which resulted in 6 additional publications. VS and OH screened titles and abstracts of these 2 310 publications, 109 studies met the inclusion criteria. After careful independent full-text screening by VS and OH, 62 studies were included in this review. The flow chart of this selection procedure is presented in Figure 2.

Bone sarcomas

Length of total interval

Thirty-four studies involving a total of 17 258 patients investigated the total interval in bone sarcoma (Table 1A)[8-41]; five of these studies prospectively collected follow-up data. A broad range in the length of the total interval was found, which varied from 9 to 120.4 weeks.

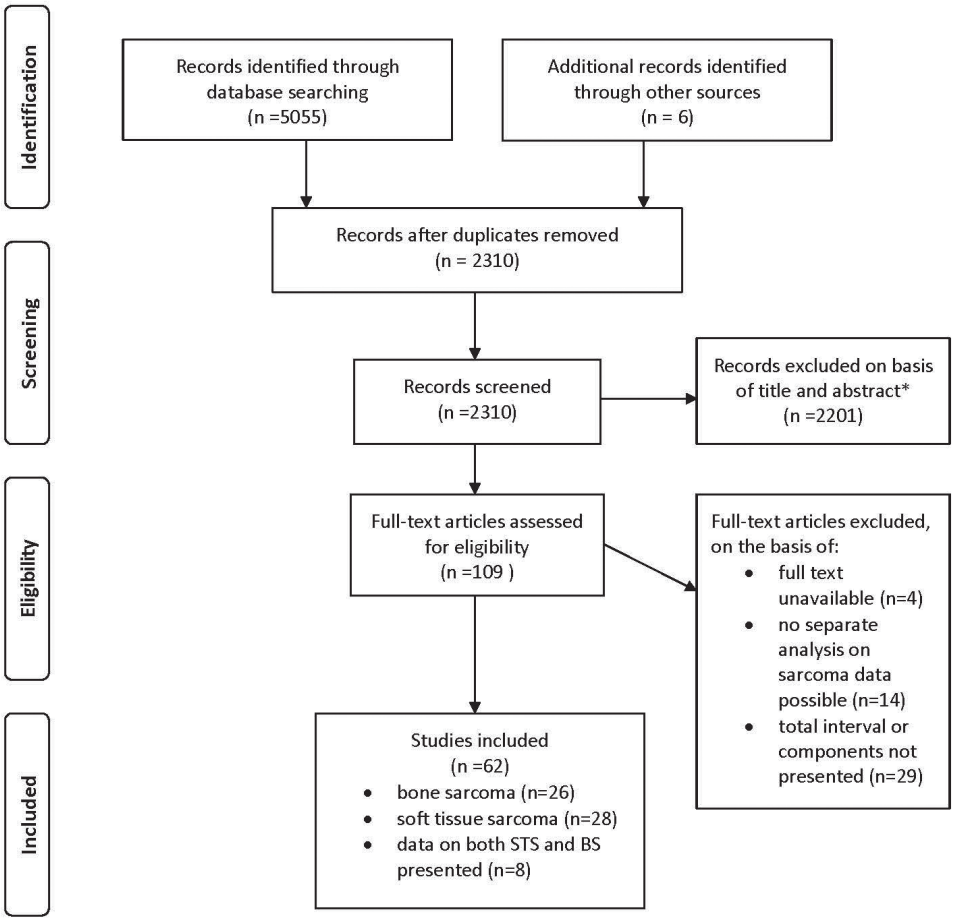

Figure 2: Selection procedure

Table 1 A: diagnostic intervals in bone sarcoma

Author; Year	Study design, inclusion period and country	Study population	Age [years]	Patient interval in weeks	Primary care interval in weeks	Secondary care interval in weeks	Tertiary care interval in weeks	Diagnostic interval in weeks	Total interval in weeks
Kammerer; 2011;	Retrospective 1972-2010 Germany	36 osteosarcoma of jaw	33.9 (2-81)[b,c]	15.9 (4.3-103.2)[b,c]	NR	NR	NR	NR	NR
Pan; 2010	Retrospective 2003-2008 Malaysia	30 osteosarcoma around the knee joint	17 (9-34)[b,c]	10 (0-49)[b,c]	5[b]	5 (0-24)[b,c]	2[b]	NR	17 (4-55)[b,c]
Widhe; 2010	Retrospective 1980-2002 Sweden	106 chest wall chondrosarcoma	57[b]	12.9 (0-507.4)[a,c]	19.35 (0.43-847.1)[a,c]	NR	NR	NR	34.4 (4.3-855.7)[a,c]
Goyal; 2004	Retrospective 1990-2002 UK	103 bone sarcoma	15 (4-22)[a,c]	4.3[a]	NR	NR	NR	6.88[a]	16.34 (4.3-197.8)[a,c]
Widhe; 2007	Retrospective 1981-2000 Sweden	26 Ewing sarcoma of the rib	16 (6-26)[a,c]	10.75 (0-43)[a,c]	12.9 (0-43)[a,c]	NR	NR	NR	NR
Widhe; 2000	Retrospective 1983-1995 Sweden	102 osteosarcoma	15.8 (5.5-29.5)[b,c]	6 (1-26)[b,c]	9 (1-52)[b,c]	NR	NR	NR	15 (2-75)[b,c]
		47 Ewing sarcoma	15.4 (2.5-26.0)[b,c]	15 (1-100)[b,c]	19 (1-72)[b,c]	NR	NR	NR	34 (3-150)[b,c]
Guerra; 2006	Retrospective 1985-2001 Brazil	198 osteosarcoma	15.7[b]	NR	NR	NR	NR	NR	22.6[b]
		55 Ewing sarcoma	12.8[b]	NR	NR	NR	NR	NR	34.8[b]
Brotzmann; 2013	Retrospective 1969-2008 Switzerland	32 bone sarcoma of the foot	NR	NR	NR	NR	NR	NR	43[a]
		15 chondrosarcoma	NR	NR	NR	NR	NR	NR	32.3[a]
		9 osteosarcoma	NR	NR	NR	NR	NR	NR	64.5[a]
		8 Ewing sarcoma	NR	NR	NR	NR	NR	NR	77.4[a]
Biscaglia; 1998	Retrospective 1983-1999 Italy	12 osteosarcomas of the foot	33 (17-64)[b,c]	50%[e]	NR	NR	NR	NR	120.4 (6-48)[b,c]

Table 1 A: Continued

Author; Year	Study design, inclusion period and country	Study population	Age [years]	Patient interval in weeks	Primary care interval in weeks	Secondary care interval in weeks	Tertiary care interval in weeks	Diagnostic interval in weeks	Total interval in weeks
Bacci; 1999	Retrospective 1979-1997 Italy	618 Ewing sarcoma	NR	13[b]	NR	NR	NR	4[b]	18[b]
Bacci; 2000	Retrospective 1983-1999 Italy	965 high-grade osteosarcoma of the extremity	NR	5.2[b]	NR	NR	NR	4.8[b]	10.5 (1-59)[b,c]
		810 localized		6.0 [b]	NR	NR	NR	NR	10.7[b]
		155 metastasized disease		4.1 [b] (p<0.00017)	NR	NR	NR	NR	9.0[b] (p<0.016)
Bacci; 2002	Retrospective 1980-1999 Italy	1071 high-grade osteosarcoma of the extremity	<15: n=501[d] ≥15: n=570[d]	NR	NR	NR	NR	NR	NR
		891 localized disease		NR	NR	NR	NR	NR	10.9[b]
		180 metastasized disease		NR	NR	NR	NR	NR	9.3[b] (p<0.0002)
Bacci; 2007	Retrospective 1983-2006 Italy	888 Ewing sarcoma family tumour	< 12: n=160[d] ≥12: n=728[d]	NR	NR	NR	NR	NR	75%[e]
Goedhart; 2016	Retrospective 2000-2012 The Netherlands	102 high-grade bone sarcoma	30.0 (5-89)[b,c]	NR	NR	NR	NR	NR	NR
		19 chondrosarcoma		34.9[b] (p<0.05)	28.2[b]	7.1[b] (p<0.05)	5[b]	NR	98,3[b]
		29 Ewing sarcoma		5.9[b]	14.8[b]	2.3[b]	3.5[b]	NR	22.9[b] (p<0.01)
		54 osteosarcoma		6.4[b]	8.3[b]	2.4[b]	3.8[b]	NR	23.3[b] (p<0.01)
Brasme; 2014	Prospective 1988-2000 France	436 Ewing sarcoma	12[a]	NR	NR	NR	NR	NR	10[a]
Kim; 2009	Retrospective 1985-2005 Korea	26 osteosarcoma and doctor delay >45 days	30.2 (4-67)[b,c]	NR	NR	NR	NR	45.2[b]	NR

Table 1 A: Continued

Author; Year	Study design, inclusion period and country	Study population	Age [years]	Patient interval in weeks	Primary care interval in weeks	Secondary care interval in weeks	Tertiary care interval in weeks	Diagnostic interval in weeks	Total interval in weeks
Simpson; 2005	Retrospective 1965-2005 Scotland	19 Ewing sarcoma of upper limb	19 (3-57)[b,c]	25.8 (4.3-774)[a,c]	NR	NR	NR	5 (1-128)[a,c]	35 [a]
Wurtz; 1999	Retrospective 1975-1995 USA	68 bone sarcoma of pelvic girdle	41 (8-82)[a,c]	NR	NR	NR	NR	NR	43[3] 25.8 (4.3-206.4)[a,c]
Sneppen; 1984	Retrospective 1962-1979 Denmark	84 osteosarcoma	28 (8-86)[b,c]	6.9[b]	NR	NR	NR	7.3[b]	27.5 (8.6 -154.8)[b,c]
		40 Ewing sarcoma	17 (2-62)[b,c]	6.5[b]				32.3[b]	41.3 (4– 206,4)[b,c]
Nandra; 2015	Retrospective 1985-2010 UK	2360 bone sarcomas	22[a]	NR	NR	NR	NR	NR	16 [a]
Vadillo; 2011	Retrospective 1952-2007 Peru	135 bone sarcomas of the jaw	31 (1-80)[b,c]	13[b]	19.7[b]	NR	17.4[b]	NR	50.1[b]
Ashwood; 2003	Prospective 1997-1998 UK	100 tumour service	36.3 [b]	63.6 (0-111.8)[b,c]	NR	NR	NR	58 (2,3-516)[b,c]	NR
		49 malignant disease: 47 sarcoma	NR	32.7 (2.2-47.3) [b,c]	32.3 (0-55.9)[b,c]	NR	NR	NR	NR
George; 2012	Retrospective 2011 UK	107 sarcoma of which	≥18 [d]	4.3[a]	NR	NR	NR	13.7[a]	NR
		41 bone sarcoma		6.5 (0 -3096)[a,c]	16.8 (1.5-211.6)[a,c]	NR	NR	NR	NR
Martin; 2007	Retrospective 2001-2003 USA	235 patients;	22.2 (15-29)[b,c]	NR	NR	NR	NR	NR	10.7[b]
		66 with sarcoma		NR	NR	NR	NR	NR	20.3[b]
		30 bone sarcoma		NR	NR	NR	NR	NR	15.7[b]
Smith; 2011	Prospective 1985-2009 UK	2568 bone sarcomas	25[a]	NR	NR	NR	NR	NR	16 [a]

Table 1 A: Continued

Author; Year	Study design, inclusion period and country	Study population	Age [years]	Patient interval in weeks	Primary care interval in weeks	Secondary care interval in weeks	Tertiary care interval in weeks	Diagnostic interval in weeks	Total interval in weeks
Grimer; 2006	Prospective 1986-2006 UK	1460 bone sarcoma	NR	NR	NR	NR	NR	NR	16 [a]
Lawrenz; 2018	Retrospective 1990-2014 UK	bone sarcoma: 1446 non-metastatic 346 metastatic	30.7[b]	NR	NR	NR	NR	NR	16[a] 45.8[b] vs 29.9[b]
Balmant; 2018	Retrospective 2007-2011 Brazil	1257 osteosarcoma and Ewing sarcoma	0-29[d]	NR	NR	NR	NR	NR	NR
			0-14[d] (46%)	NR	NR	NR	NR	1.1[a]	NR
			15-19[d] (33%)	NR	NR	NR	NR	1.3[a]	NR
			20-29[d] (21%)	NR	NR	NR	NR	1.9[a]	NR
Bielack; 2002	Retrospective 1980-1998 German/Austrian/ Swiss	1702 high grade osteosarcomas	16.7[c]	NR	NR	NR	NR	9.9[a]	NR
Chen; 2017	Retrospective 2004-2012 USA	364 malignancies of which 30 bone sarcoma	16.5[a]	NR	NR	NR	NR	NR	12.4[a]
Desandes; 2018	Retrospective 2012-2013 France	993 malignancies of which 48 bone sarcoma	NR	NR	NR	NR	NR	NR	NR
			15-19 (n=33)[d]	NR	NR	NR	NR	NR	10.1[a]
			20-24 (n=15)[d]	NR	NR	NR	NR	NR	21.4[a]
Petrilli; 2006	Prospective 1987-1996 Brazil	209 high grade osteosarcomas	14 (2.4-24.5)[b,c]	NR	NR	NR	NR	NR	18.4[b]
Yang; 2009	Retrospective 1994-2005 Hong Kong	51 osteosarcoma	13 (3-20)[a,c]	4.3 (0-51.4)[a,c]	NR	NR	NR	3 (0-50)[a,c]	8.7 (0-51.6)[a,c]
Younger; 2018	Retrospective 2015 UK	558 sarcoma of which 140 bone sarcoma	64.1 (18-96)[b,c]	56.7%[e]	NR	NR	NR	NR	NR

NR= not reported; [a]= median; [b]=mean; [c]= range within brackets; [d]=included age group; [e]=% of delays attributed to this interval.

Components of the total interval

The impact of patient intervals was measured in 19 studies (mean 4.1 to 34.1 weeks), eight studies measured the primary care interval (mean 5 to 32.3 weeks), whereas the secondary (mean 2.3 to 7.1 weeks) and tertiary care intervals (mean 2 to 17.4 weeks) were measured in two and three studies respectively(Table1).

Effect of tumour specific factors

Several factors were studied as determinants of the length of the total interval. Interestingly, tumour specific factors such as tumour size or grade did not appear to influence the length of total interval[22, 26, 27, 41]. Patients with sarcomas located in the trunk were shown to have a longer interval than those who have sarcomas in the extremities (29 versus 14 weeks; $p<0.001$) by Lawrenz et al. (n=1792)[41].

Tumour histology was found to be of influence on the total interval. Goedhart et al. performed a retrospective study among 102 patients with high-grade bone sarcoma and reported a significantly longer patient interval and secondary care interval for chondrosarcoma versus Ewing sarcoma and osteosarcoma[21], which resulted in a significantly longer total interval, with a mean of 98.3 weeks for chondrosarcoma, versus 22.9 and 23.3 weeks for Ewing sarcoma and osteosarcoma respectively.

Four other studies reported similar results on total intervals for Ewing sarcoma and osteosarcoma; all had a trend towards a longer diagnostic pathway for patients with Ewing sarcoma[12, 14, 26, 40]. In a study by Widhe et al. (n=106), the longer diagnostic pathway in Ewing sarcoma was a result of both a longer patient and primary care component[11], whereas a study by Sneppen et al. (n=124), reported a four times longer diagnostic interval for Ewing sarcoma than for osteosarcoma patients despite similar patient intervals[25]. Lawrenz et al. illustrated that intermediate-grade tumours had a longer diagnostic interval (52 weeks) compared with high-grade bone sarcomas (12 weeks; $p<0.001$)[41]. In contrast, a study focusing only on bone sarcoma of the foot (n=32) presented opposite results: a median total interval of 32.3 weeks for chondrosarcoma, versus 64.5 weeks and 77.4 weeks for osteosarcoma and Ewing sarcoma respectively[15]. Another small study (n=6) reported that half of patients with osteosarcoma of the foot had a considerable patient delay, resulting in a mean total interval of 120.4 weeks[16].

Effect of patient specific factors

Gender was not associated with the length of the total interval in four studies[12, 26, 39, 40], however there was evidence that patient age was a factor. Six studies reported a significantly longer total interval for older teenagers, adolescents or adults compared to younger children or (younger) teenagers (<12 versus ≥12-22 years[11, 22]; <20 versus ≥20-86 years[26]; <22 versus ≥ 22 years[27]; 0-14 versus 15-19 versus 20-29 years[40]; <12

versus ≥12 years[11]). Furthermore, Desandes et al. found young adults were more at risk for a longer total interval than patients in puberty (15-19 versus 20-24 years; 10.1 versus 21.4 weeks respectively; p=0.04)[35]. Lawrenz et al.(n=1792) investigated age (mean 30.7 years) as a continuous variable and reported every additional year of age was associated with a 1.3 week longer total interval(p<0.00)[41]. In contrast Guerra et al. (n=253) found no significant relationship between age (range 0-30 years) and the length of the total interval[14]. Younger et al. found no relationship between age and patient interval nor diagnostic interval[38].

The presenting symptom did not predict the length of the total interval in four studies[12, 13, 22, 26]. Study results (n=4) on the influence of pain symptoms on the total interval are contradictory, with some studies suggesting a shortening of the interval, no influence, or even a longer total interval[12, 13, 22, 26]

Effect of healthcare system related factors

The influence of the year of first presentation was studied in five studies. None showed evidence of shortening total intervals over the past 30 to 50 years[10, 14, 22, 26, 41], despite advances in healthcare models including the introduction of cancer pathways and dedicated specialist sarcoma centres.

The location of first presentation to a healthcare professional was investigated among patients with Ewing sarcoma. The diagnostic interval was significantly longer when presenting to a general practitioner (GP) compared with the Accident & Emergency department (p=0.04)[11].

The influence of radiology and pathology investigations on the diagnostic interval were reported in two studies[10, 12]. When no imaging studies were ordered at the patient's first contact with a healthcare professional, a longer diagnostic interval was observed. When imaging was incorrectly interpreted as normal, which was the case in 35% of patients with chondrosarcoma at non-specialist centres, this resulted in an even longer diagnostic interval (21 versus 9.5 months). At non-specialist centres, only 26% (n=39) of chondrosarcomas biopsied were correctly diagnosed as malignant, whilst at specialist sarcoma centres, 94% (n=34) were correctly diagnosed[10]. A descriptive study by Ashwood et al. highlighted how imaging studies performed prior to referral to a specialist centre often had to be repeated because they did not provide all the required information, and biopsies or surgeries performed by the referring teams often complicated the patient's subsequent management[29].

A qualitative study in Malaysia by Pan et al. (n=30) demonstrated the multifactorial nature of diagnostic delay, which was dependent on the patient perception of symptoms and complaints, the influence of traditional healers, and the proximity of health clinics[9]. A Brazilian study with 1257 bone sarcoma patients found differences in diagnostic intervals between geographic regions, possibly explained by the availability of CT scan equipment and the difference in number of hospital beds per region[40].

Relationship between total interval and outcomes

The influence of delay on clinical outcomes of bone sarcoma patients has been investigated in 20 of the 34 included bone sarcoma studies(Table 1B)[10, 11, 15, 17-25, 27, 28, 31, 33, 36, 37, 39, 41].

In twelve of these studies (n=7,414), no significant association between length of the total interval (mean total interval between 8.7 and 50.1 weeks) and overall survival was found[11, 15, 19, 21, 22, 25, 27, 28, 33, 36, 37, 39]. However, one of these studies (n=1,702) found that patients with a longer total interval more often had metastatic disase at diagnosis than those with a short total interval[39].

One study of 965 high grade osteosarcomas of the extremities diagnosed between 1983-1999, identified an inverse relationship between the total interval and the stage of disease [19]; the patient interval was significantly shorter in patients with metastatic disease compared to patients with localized disease (4.1 versus 6.0 weeks), ultimately resulting in a shorter total interval (9.0 versus 10.7 weeks). The total interval was significantly shorter in patients who later relapsed than in patients who remained free of disease after 5 years. However, this difference lost significance when patients were analysed according to disease stage at presentation. In a secondary analysis of this patient population, including patients diagnosed between 1980-1983 (n=1,071)[18], patients with a diagnostic interval <2 months were significantly more likely to have metastases at diagnosis than those with a longer interval (56.1% versus 45.2%; $p<0.0009$).

Two other studies by the same research group in patients with Ewing sarcoma and Ewing sarcoma family of tumours (ESFT), both demonstrated that a diagnostic interval <2 months was associated with an increased likelihood of metastases at diagnosis (Table 1B) [17, 20], impact on overall survival was not reported.

A study with 1,792 bone sarcoma patients showed that a longer duration of symptoms was associated with longer survival (HR 0.996, 95% confidence interval (CI) 0.994-0.998) [41]. This continuous association was lost when patients were compared in categories(< or > 4 months; HR 0.935 95% CI 0.743-1.177).

Table 1 B: the effect of diagnostic interval on stage or metastases at diagnosis, or overall survival for bone sarcomas

Author; Year	Study design, inclusion period and country	Study population	Age [years]	Total interval in weeks	Stage of disease or metastases at diagnosis	Overall survival
Widhe; 2010	Retrospective 1980-2002 Sweden	106 chest wall chondrosarcoma	57[b]	34.4 (4.3-855.7)[a,c]	NR	Patients who died from chondrosarcoma had interval > 8 months (p<0.05)
Goyal; 2004	Retrospective 1990-2002 UK	103 bone sarcoma	15 (4-22)[a,c]	16.34 (4.3-197.8)[a,c]	NR	No association
Brotzmann; 2013	Retrospective 1969-2008 Switzerland	32 bone sarcoma of the foot	NR	43[a]	No association	No association
Bacci; 1999	Retrospective 1979-1997 Italy	618 Ewing sarcoma	NR	18 [b]	Stage: no association Interval <2 months, more metastases (32 vs 12% p<0.0001)	
Bacci; 2000	Retrospective 1983-1999 Italy	965 high-grade osteosarcoma extremity	NR	10.5 (1-59)[b,c]	NR	No association
Bacci; 2002	Retrospective 1980-1999 Italy	high-grade osteosarcoma extremity	<15: n=501[d] ≥15: n=570[d]			NR
		891 localized disease		10.9[b]	45.2% diagnostic interval <2 months	
		180 metastasized disease		9.3[b] (p<0.0002)	56.1% diagnostic interval <2 months (p<0.0009)	
Bacci; 2007	Retrospective 1983-2006 Italy	888 Ewing sarcoma family tumour	< 12: n=160[d]	<2 months: n=215[d]	35.5% metastatic disease	NR
			≥12: n=728[d]	≥2 months: n=658[d]	15.9% metastatic disease (p<0.0001)	NR
Goedhart; 2016	Retrospective	19 chondrosarcoma	30.0 (5-89)[b,c]	98,3[b]	**Metastatic disease** 10.5%	**5 year overall survival** 60.9%
	2000-2012 The Netherlands	29 Ewing sarcoma		22.9[b] (p<0.01)	37.9%	49%
		54 osteosarcoma		23.3[b](p<0.01)	24.1%	67%
Brasme; 2014	Prospective 1988-2000 France	436 Ewing sarcoma	12[a]	10[a]	No association	No association

Table 1 B: Continued

Author; Year	Study design, inclusion period and country	Study population	Age [years]	Total interval in weeks	Stage of disease or metastases at diagnosis	Overall survival
Kim; 2009	Retrospective 1985-2005 Korea	26 osteosarcoma and doctor delays >45 days	30.2 (4-67)[b,c]	NR	NR	**5 year overall survival:** 26% **10 year OS:** 10%
Simpson; 2005	Retrospective 1965-2005 Scotland	19 Ewing sarcoma of upper limb	19 (3-57)[b,c]	35[a]	A higher Enneking stage resulted in greater mortality (p=0.02)	NR
Wurtz; 1999	Retrospective 1975-1995 USA	68 bone sarcoma of pelvic girdle	41 (8-82)[a,c]	43[c]	No association	No association
Nandra; 2015	Retrospective 1985-2010 UK	2668 bone sarcoma	22[a]	16[a]	No association	No association
Vadillo; 2011	Retrospective 1952-2007 Peru	135 bone sarcoma of the jaw	31 (1-80)[b,c]	50.1[b]	NR	No association
Martin; 2007	Retrospective 2001-2003 USA	30 bone sarcoma	22.2 (15-29)[b,c]	15.7[b]	Osteosarcoma: diagnostic interval 259 days longer for patients with advanced stage disease than those with localized disease (p<0.01)	NR
Grimer; 2006	Prospective 1986-2006 UK	1460 bone sarcoma	NR	16[a]	NR	No association
Lawrenz; 2018	Retrospective 1990-2014 UK	bone sarcoma 1446 non-metastatic 346 metastatic	30.7[b]	16[a] 45.8[b] vs 29.9[b]	No association p=0.009	Non-metastatic cohort: longer interval, better survival (HR 0.996). No association > or < 4 months.
Bielack; 2002	Retrospective 1980-1998 German/Austrian/Swiss	1702 high grade osteosarcoma	16.7[b]	9.9[a]	Longer diagnostic interval: more primary metastases (p=0.007)	No association
Petrilli; 2006	Prospective 1987-1996 Brazil	209 high grade osteosarcoma	14 (2.4-24.5)[b,c]	18.4[b]	No association	No association
Yang; 2009	Retrospective 1994-2005 Hong Kong	51 osteosarcoma	13 (3-20)[a,c]	8.7 (0-51.6)[a,c]	No association	No association

NR= not reported; [a]= median; [b]=mean; [c]= range within brackets; [d]=included group.

In contrast, four studies with a combined number of 386 patients with chondrosarcoma, osteosarcoma and Ewing sarcoma, and mean total intervals between 10.7 and 35 weeks, reported a negative impact of a long total interval on stage and survival[10, 23, 24, 31].

No study has reported on the association between length of the total interval on patient reported outcomes including HRQoL.

Soft tissue sarcoma

Length of total interval

Thirty-six studies investigated the total interval for soft tissue sarcoma (Table 2A)[27, 30-35, 38, 42-69]. A combined total of 16 845 patients were included and, reflecting soft tissue sarcoma (STS) heterogeneity, the total interval varied tremendously; between 4.3 to 614.9 weeks.

Components of the total interval

Eleven studies examined the length of one or more components of the total interval[30, 38, 44, 47, 50-52, 54, 58, 59, 63]. Patient intervals varied between a median of 1.3 to 17.2 weeks, the primary care interval lasted 0.1 to 13.3 weeks, the secondary care interval varied between 1.1 and 6.9 weeks and the tertiary care interval was 2.1 to 7.9 weeks.

Effect of tumour specific factors

Three studies found no relationship between tumour size and length of the total interval[27, 54, 69], one study (n=575) in children and adolescents found that larger tumours were associated with a longer total interval (both for tumours <5 versus ≥5cm and <10 versus ≥10cm)[67], whilst a study in adults (n=162) reported that smaller tumours (median 8cm) were associated with a longer total interval[47].

Five studies reporting on the influence of tumour localization have yielded contradictory results. Chotel et al. (n=33) reported that synovial sarcoma of the knee or elbow had a longer total interval than tumours at other sites[54] and Smolle et al. found synovial sarcomas located superficially had a longer interval than deeply located tumours (n=248; 2 years versus 12 months)[68]. However, two other studies found no relationship between tumour site and total interval[47, 69]. In children and adolescents, Ferrari et al. (n=575) reported a longer total interval for soft tissue sarcomas of the extremities compared to tumours at other sites[67]; the authors attributed this difference to the underlying tumour histology, which for extremity tumours was more likely to consist of non-rhabdomyosarcomas and thus to encompass a broad spectrum of tumour biologies including low grade soft tissue sarcomas. There is limited data specifically exploring the relationship between tumour histology and total interval, but Nandra et al. (n=2 277) identifed that low grade sarcomas were associated with a longer total interval[27] .

Table 2A: length of diagnostic intervals for soft tissue sarcomas

Author; Year	Study design, time period and country	Study population	Age [years]	Patient interval [weeks]	Primary care interval [weeks]	Secondary care interval [weeks]	Tertiary care interval [weeks]	Diagnostic interval [weeks]	Total interval [weeks]
Gofman; 2007	Retrospective 1991-2004 Israel	73 synovial sarcoma	38 (8-82)[a,c]	NR	NR	NR	NR	NR	77.4 (8.6-202.1)[a,c]
Amant; 2003	Retrospective 1990-2002 Belgium	6 endometrial stromal sarcoma	34[a]	NR	NR	NR	NR	NR	614.9 (103.2-1754.4)[a,c]
Nakamura; 2011	Retrospective 2001-2009 Japan	100 STS, referred for additional resection	57 (0-89)[b,c]	12.9 (4.3-309.6)[a,c]	NR	NR	NR	15%[e]	25.8(4-310))[a,c]
Pawlik; 2003	Retrospective 1975-2002 USA	29 angiosarcoma of the scalp	71[a]	NR	NR	NR	NR	NR	21.9 (0-73.5)[a,c]
Rougraff; 2012	Retrospective 1992-2007 USA	381 grade 3 STS of extremity or flank	NR	NR	NR	NR	NR	NR	66.6[b] 20[a]
Rougraff; 2006	Retrospective 1992-2003 USA	624 sarcoma: 382 soft-tissue sarcoma	NR	NR	NR	NR	NR	NR	NR
		278 high-grade STS							73.3 (0.25-362.8)[b,c]
		104 low-grade STS							127.4 (0.25-256)[b,c]
Singla; 2014	Retrospective 1990-2011 USA	72 angiosarcoma	65 (19-93)[a,c]	NR	NR	NR	NR	NR	0-154.8[c] 41%[e]
Ferrari; 2010	Retrospective 1977-2005 Italy	575 STS	≤21[d]	NR	NR	NR	NR	NR	8.6 (1-258)[a,c]
Pratt; 1978	Retrospective 1962-1976 USA	46 rhabdyomyosarcoma of head or neck	5.9 (0.3-20.5)[a,c]	NR	NR	NR	NR	NR	4.3 - 19.3[a]
Bandyopadhyay; 2016	Retrospective 1991-2010 USA	391 primary pulmonary artery sarcoma	52 (14-94)[a,c]	NR	NR	NR	NR	NR	14.3[a]

Table 2A: Continued

Author; Year	Study design, time period and country	Study population	Age [years]	Patient interval [weeks]	Primary care interval [weeks]	Secondary care interval [weeks]	Tertiary care interval [weeks]	Diagnostic interval [weeks]	Total interval [weeks]
Brouns; 2003	Retrospective 1999-2001 Belgium	100 STS	50.5 (3-88)[a,c]	17.2 (8.6-1032)[a,c]	NR	NR	NR	25.8 (8.6-339.7)[a,c]	NR
Chandu; 2003	Retrospective 1955-1999 Scotland	109 STS	33.4 (10-77)[b,c]	NR	NR	NR	NR	86[b]	NR
Clark; 2005	Prospective 2003-2004 UK	31 STS with referral >3 months (19.5%)	59 (34-84)[b,c]	NR	NR	NR	NR	94.6 (17.2-412.8)[b,c]	NR
Johnson; 2008	Prospective/recall 2005 UK	162 STS	53 (16-88)[b,c]	1.3[a] 28.6[b]	2.4[a]	6.9[a]		25.0[a] 83.1[b]	40.4[a] 112.3[b]
Lawrence; 1986	Retrospective 1977-1978 and 1983-1984	2355 STS and 3457 STS	>18[d]	NR	NR	NR	NR	4.3[a]	17.2[a]
Park; 2010	Retrospective 1997-2008 Korea	18 grade 3 STS of the extremity with delay > 1 year	44.8 (15-79)[b,c]	NR	NR	NR	NR	NR	(51.6-154.8)[c]
Seinen; 2010	Retrospective 2003-2009 Sweden	33 retroperitoneal sarcoma (1 GIST)	66 (21-86)[b,c]	3.3 (0-73.1)[a,c]	2.1 (0-34.9)[a,c]	5.1 (0.3-160)[a,c]	1.1(0.1-69)[a,c]	13.4 (4.3-172)[a,c]	NR
Bruun; 1976	Retrospective 1962-1974 Denmark	7 oral sarcoma	29 (10-81)[b,c]	6.9[b]	NR	NR	NR	15.9[b]	NR
Cooper; 1996	Retrospective 1984-1993 Ireland	18 STS interval > 4 weeks	43 (2-89)[a,c]	36%[e]	23%[e]	11%[e]	NR	28[a]	NR
Antillon; 2008	Retrospective 2000-2007 Guatemala	47 rhabdo-myosarcoma	6 (1-17)[a,c]	NR	NR	NR	NR	NR	8.6 (2– 51.6)[a,c]
		33 nonrhabdo-myosarcoma	11 (2-17)[a,c]						25.8 (3– 154.8)[a,c]

Table2 A: Continued

Author; Year	Study design, time period and country	Study population	Age [years]	Patient interval [weeks]	Primary care interval [weeks]	Secondary care interval [weeks]	Tertiary care interval [weeks]	Diagnostic interval [weeks]	Total interval [weeks]
Chotel; 2008	Retrospective 1985-2006 UK	33 synovial sarcoma	12.3 (3-16)[b,c]	43 (0-156)[b,c]	NR	NR	NR	50 (0-362)[b,c]	98 (2-364)[b,c]
Durve; 2004	Retrospective 1980-2000 UK	14 rhabdo-myosarcoma of ear and temporal bone	4.5 (1.0-8.6)[b,c]	NR	NR	NR	NR	NR	21 (4-78)[b,c]
Watson; 1994	Retrospective 1985-1992 Australia	40 STS of extremity	59 (14-87)[a,c]	NR	NR	NR	NR	NR	16 weeks (2-104)[a,c]
Monnier; 2005	Retrospective 1982-2002 France	66 dermatofibrosarcoma protuberans	43 (8-81)[b,c]	NR	NR	NR	NR	NR	520.1 (8.3-2115.6)[b,c]
Dyrop; 2013	Retrospective 2007-2010 Denmark	258 STS	NR	NR	NR	NR	2007: 4[a] 2010: 2.6[a]	NR	NR
Buvarp Dyrop; 2016; 2017	Retrospective 2014-2015 Denmark	545 referred patients of which:	55 (0-93)[a,c]	NR	NR	NR	NR	NR	NR
		102 sarcoma patients (88 soft tissue 14 bone)		11[a]	2.4[a]	4.1[a]	2.4[a]	NR	25.1[a]
George; 2012	Retrospective 2011 UK	66 STS	≥18[d]	4.3 (0-516)[a,c]	13.3 (1.7-154.8)[a,c]	NR	NR	NR	NR
Martin; 2007	Retrospective 2001-2003 USA	38 STS	22.2 (15-29)[b,c]	NR	NR	NR	NR	NR	24.9[b]
Smith; 2011	Prospective 1985-2009 UK	2366 STS	57[a]	NR	NR	NR	NR	NR	26[a]
Grimer; 2006	Prospective 1986-2006 UK	1460 STS	NR	NR	NR	NR	NR	NR	26[a]

Table 2A: Continued

Author; Year	Study design, time period and country	Study population	Age [years]	Patient interval [weeks]	Primary care interval [weeks]	Secondary care interval [weeks]	Tertiary care interval [weeks]	Diagnostic interval [weeks]	Total interval [weeks]
Chen; 2017	Retrospective 2004-2012 USA	364 malignancies of which 18 STS	14[a]	NR	NR	NR	NR	NR	7.2[a]
Nandra; 2015	Retrospective 1985-2010 UK	2277 STS	57[a]	NR	NR	NR	NR	NR	26[a]
Desandes; 2018	Retrospective 2012-2013 France	993 malignancies of which 43 STS	NR	NR	NR	NR	NR	NR	22.9[a]
			15-19 [b]	NR	NR	NR	NR	NR	15.4[a]
			20-24[b]	NR	NR	NR	NR	NR	48.7[a]
Smolle; 2019	Retrospective 1982-2014 UK	248 synovial sarcomas	37[b]	NR	NR	NR	NR	NR	52[a]
			<16[d]	NR	NR	NR	NR	NR	49.8[a]
			≥16[d]	NR	NR	NR	NR	NR	52[a]
Younger; 2018	Retrospective 2015 UK	558 sarcoma of which 418 STS	64.1 (18-96) [b,c]	46.8%[e]	NR	NR	NR	NR	NR

NR= not reported; [a]= median; [b]=mean; [c]= range within brackets; [d]=included age group; [e]=% of delays attributed to this interval

Effect of patient specific factors

Patient gender, level of education and measures of social deprevation were not associated with length of total interval[47, 67]. The effect of patient age was examined in five studies. Ferrari et al.(n=575) established that children over 10 years old had a longer total interval than those younger than 10 years old[67]. Desandes et al. (n=43) found the same result when comparing age groups 15-19 versus 20-24 years (15.4 versus 48.7 weeks; p=0.04) [35]. Smolle et al. found no difference for patients with synovial sarcoma older or younger than 16 years old[68]. A large retrospective study of almost 5,000 sarcoma patients found no difference in total interval in patients older and younger than the median study age of 57 years[27]. A Sarcoma UK survey (n=558) established no association between age and patient interval or total interval[38].

Two studies in children examined the effect of presenting symptoms on the total interval. The first (n=575) found no significant difference in the length of total interval between patients presenting with a swelling or with a specific symptom (e.g. urethral obstruction) [67]. The second in 33 patients with synovial sarcoma, found the presence of a lump led to a shorter doctor interval, whilst a peri-articular location or presence of a joint contracture led to both a longer patient and a longer doctor interval[54].

Effect of healthcare system related factors

The influence of the year of first presentation was studied in two publications, which did not find an improvement in total interval over the past 30 to 40 years[54, 67].

In a study of 162 STS patients surveyed in 2005, the median patient interval was just 1.3 weeks, whilst the median primary care interval was 25.0 weeks[47]; if patients were reassured by the first medical professional they consulted (e.g. their general practitioner), it took twice as long to be referred on to an appropriate specialist centre.

Another single centre study of 545 patients with suspected sarcoma referred to a specialist clinic in Denmark reported a median total interval of 25.1 weeks[59]; 102 patients (19%) had a sarcoma (88 soft tissue, 14 bone sarcoma), 68 patients (12%) had another malignancy[58]. Patients referred to the centre with prior investigations in their local hospital had a longer total interval than those with investigations in the sarcoma centre (median 13.3 versus 23.7 weeks). Synovial sarcoma patients with an unplanned resection had a longer diagnostic interval than those referred directly to a sarcoma centre (24 versus 12 months; p=0.001)[68].

Relationship between total interval and patient outcomes

The influence of the length of total interval on clinical outcomes in soft tissue sarcoma patients has been reported in ten retrospective studies(Table 2B)[27, 43, 54, 61-63, 65, 67-69].

Table 2 B: The influence of length of the total interval on outcomes for soft tissue sarcomas

Ref.	Study design, time period and country	Study population	Age [years]	Total interval [weeks]	Influence on stage or metastases at diagnosis	Influence on survival
Gofman; **2007**	Retrospective 1991-2004 Israel	73 synovial sarcoma	38 (8-82)[a,c]	77.4 (8.6-202.1)[a,c]	NR	Total interval ≤1 year resulted in better systemic control (HR 0.3; p=0.037). No effect on overall survival.
Amant; **2003**	Retrospective 1990-2002 Belgium	15 endometrial stromal sarcoma	34[b]	NR	Stage 4 disease in 5/6 with missed diagnosis, compared to 1/9 in correct diagnosis group. No data on diagnostic interval in the latter group.	NR
		6 (40%) diagnosis initially missed		614.9 (103.2-1754.4)[b,c]		
Nakamura; **2011**	Retrospective 2001-2009 Japan	100 STS, referred for additional resection	57 (0-89)[b,c]	25.843-17)[a,b]	NR	5 years survival: 54.4% (66.8% without metastases, 5.9% with metastases)
				> 6 months: n=43[d]	12/43 metastases versus	59.7% (34 patients without metastases) (p=0.04)
				≤6 months: n=57[d]	6/51 metastases (p=0.048)	77% (48 patients without metastases)
Rougraff; 2012	Retrospective 1992-2007 USA	381 grade 3 STS of extremity or flank	NR	66.6[b] 20[a]	No association	No association
Rougraff; **2006**	Retrospective 1992-2003 USA	624 sarcoma: 382 soft-tissue sarcoma	NR	NR	No association	No association
		278 high-grade STS		73.3 (0.25-362.8)[b,c]		
		104 low-grade STS		127.4 (0.25-256)[b,c]		
Ferrari; **2010**	Retrospective 1977-2005 Italy	575 STS	≤21[d]	8.6 (1-258)[a,c]	No association	Risk of death increased the longer the diagnostic interval (p=0.002)
Bandyopadhyay; **2016**	Retrospective 1991-2010 USA	391 primary pulmonary artery sarcoma	52 (14-94)[a,c]	14.3[a]	NR	For every doubling diagnostic interval, the odds of death increased by 46% (p<0.001)
Chotel; **2008**	Retrospective 1985-2006 UK	33 synovial sarcoma	12.3 (3-16)[b,c]	98 (2-364)[b,c]	NR	No association

Table 2 B: Continued

Ref.	Study design, time period and country	Study population	Age [years]	Total interval [weeks]	Influence on stage or metastases at diagnosis	Influence on survival
Nandra; **2015**	Retrospective 1985-2010 UK	2277 STS	57[a]	NR	No association	1 year mortality (13%), survivors longer total interval (20 versus 26 weeks)
Smolle; 2019	Retrospective 1982-2014 UK	248 synovial sarcomas	37[b]	52[a]	NR	No association (<1 year versus >1 year)
			<16[d]	49.8[a]		
			≥16[d]	52[a]		

NR= not reported; [a]= median; [b]=mean; [c]= range within brackets; [d]=included group of patients;

Five of these studies observed no effect on survival[54, 61, 65, 68, 69]. One study (n=2 277) reported that patients with soft tissue sarcoma treated between 1985 and 2010 with a longer total interval (26 vs 20 weeks) had a significantly improved survival rate, even when stratified by disease stage[27]. This pattern was consistent for all histological subtypes apart from rhabdomyosarcoma where survival was significantly better with a short total interval (n=34, 16 versus 52 weeks total interval). Furthermore, patients undergoing unplanned resections prior to specialist referral had a lower 1-year mortality rate than patients referred directly. These patients tended to have small, superficial, low grade tumours, which are associated with a better prognosis.

Three studies reported that patients with a shorter total interval had improved overall survival rates[43, 63, 67]. Ferrari et al. analysed the risk of death for 575 children at different time intervals and found worse survival with increased diagnostic interval and with diagnostic intervals <1 month versus 1 – 3 months (hazard ratio 1.4 (95% CI 0.7-2.6)) and <1 month versus >12 months (hazard ratio 3.6 (95% CI 1.7-8.0)) respectively[67]. Bandyopadhyay et al. (n=391) reported that the odds of death increased by 46% for every doubling of the diagnostic interval[43].

No study has investigated the influence of the length of the total interval on patient reported outcomes.

Discussion

This is the first systematic review on the sarcoma total diagnostic interval. Analysis of the length of the total interval is complex, as it is influenced by many different factors. In sarcomas, assessment of the total interval is further challenged by the heterogeneity of the disease,the rarity of the group and the presence of 70+ subtypes.

Focussing on the patient interval, it might be anticipated that patients who consult a doctor early have a reason for doing so (e.g. worrying, severe symptoms or evidence of rapid progression), which would result in a quicker referral for investigation and a shorter diagnostic interval[16, 21], and vice versa[12, 13, 26, 54]. However, some aspecific symptoms such as pain have given contradictory results[22, 26].

Both patient and doctor intervals might be influenced by the biological behaviour of the sarcoma. The usually indolent chondrosarcomas had a longer total interval than the more aggressive osteo- and Ewing sarcomas[12, 14, 21, 26], and non-rhabdomyosarcoma soft tissue sarcomas had a longer total interval than rhabdomyosarcomas or soft tissue ESFT[67].

Furthermore, tumour location influences the length of the total interval, with atypical tumour presentations increasing the difficulties in diagnosis and prolonging the diagnostic interval.

There are two main findings from studies of the primary and secondary care intervals. Firstly, if at initial presentation the assessing clinician is falsely re-assured or makes an incorrect diagnosis, the diagnostic interval is severely prolonged[47, 62]. Secondly, patients undergoing an unplanned resection prior to referral to a specialist centre have a lower 1-year mortality rate than those referred directly to a specialist centre[27]. This finding may be due to selection bias, as patients undergoing unplanned resections have smaller, superficial and lower grade tumours, which are known factors associated with a better prognosis.

The influence of the length of the total interval on clinical outcomes remains unclear. It might be predicted that sarcomas with more aggressive behaviour have a shorter total interval and worse survival outcomes, whilst sarcomas with indolent behaviour have a longer total interval and improved survival. Alternatively, it may be expected that shorter total intervals lead to earlier treatment and better outcomes. For STS, we found conflicting results, which is not surprising with over 70 histological subtypes with different clinical behaviours. Most bone sarcoma studies from our review not report an association between length of total interval and survival as well. Researchers have argued that this lack of an association, often reffered to as the 'waiting-time paradox', may be due to the fact that the studies have not been able to adjust for the aggressiveness of the tumour.

To date, the influence of total interval on morbidity, HRQoL and other patient reported outcomes has not been assessed. Based on the available literature in other malignancies, improving the total interval will likely influence the level of patient satisfaction, fear and morbidity. The importance of these outcomes is demonstrated by Mesko et al. who studied factors most commonly causing litigation in sarcoma cases in the USA[70]. In 81% of cases a delay in diagnosis was part of the complaint, a further 7% were about misdiagnosis and 11% about unnecessary amputation. Primary care doctors and orthopaedic specialists were most common defendants in delay in diagnosis cases.

In neither bone or soft tissue sarcoma did our review identify a clear cut-off point for appropriate versus inappropriate length of total interval or its components. Apart from the contradictory results in terms of influence of the length of the interval on survival, several other factors make it difficult to draw firm conclusions. Firstly, the design of most studies was retrospective, increasing the chance of recall bias with regard to self-reported outcomes such as dates of first symptoms. Secondly, many studies included a small number of heterogeneous patients, which made them unsuitable for subtype analysis. Although we excluded case reports, we included case series because they reflect the sort

of research that has been done in this area, and show how heterogeneous the population is. Thirdly, the inclusion criteria of studies differed; some studies only considered those patients who reported a diagnostic delay, which made it impossible to compare this group to the entire sarcoma population. Furthermore, diagnostic delay was defined differently throughout the literature. One of the limitations of this review is that we had to work with these different definitions,which made comparisons difficult. We propose for future reports that the date of pathologic diagnosis is used as the endpoint of the diagnostic interval. Furthermore, studies included in this review were conducted over the past 50 years. During this period, radiologic and histologic diagnostic techniques have evolved,treatment options have improved, and, in some countries, diagnostic pathways with referrals of suspected lumps to centralised sarcoma services have developed, which may have influenced our results.

Centralised sarcoma care may improve diagnostic pathways and there is an increasing number of (inter)national guidelines for the diagnosis and management of sarcomas[71-74]. Centralizing care at sarcoma centres with a multidisciplinary team improves the diagnostic interval because patients 1) do not lose time at local hospitals, 2) receive appropriate imaging for tumour staging and 3) get a higher rate of correct pre-operative pathologic diagnosis[10, 12, 29, 30, 50, 58, 75-79]. Improvement of these factors decrease tumour size and stage at diagnosis, resulting in an increase of the quality of surgery and improvement of survival outcomes in several of these studies[60, 75, 77-80]. . Best practices of different countries could be integrated to develop the optimal diagnostic pathway. In order for such guidelines to be successfully implemented, one needs strong political support with continuous attention to raise awareness and optimize the system by following a quality and control cycle[60].

Conclusion

This review confirms the complexity of the total interval to sarcoma diagnosis. Published studies give contradictory results in terms of determinants for a long total interval as well as its influence on outcomes. The impact of a long interval on HRQoL has not been studied. To present a clinically relevant cut-off point that discriminates between a short or long interval is thus impossible. Such a cut-off point , which can differ between histological subtypes, is necessary to make guidelines more evidence based, help to guide patients and support the sarcoma diagnostic process. Furthermore, to improve care we need to understand the impact of the total interval on HRQoL of patients diagnosed with a sarcoma. Future research should include relevant outcomes for patients , as well as focus on areas where a change in management could make a difference, such as in increased public awareness, education of primary and secondary healthcare providers and improved access to specialist centres.

Supplementary material A

Search: (((((((“Sarcoma”[Mesh]) OR (“Bone Neoplasms”[Mesh:noexp]) OR (“Soft Tissue Neoplasms”[Mesh:noexp]) OR (“Gastrointestinal Stromal Tumors”[Mesh]) OR (Sarcoma*[tiab] OR Adenosarcoma*[tiab] OR Carcinosarcoma*[tiab] OR Chondrosarcoma*[tiab] OR Desmoplastic Small Round Cell[tiab] OR Endometrial Stromal[tiab] OR Fibrosarcoma*[tiab] OR Dermatofibrosarcoma*[tiab] OR Neurofibrosarcoma*[tiab] OR Hemangiosarcoma*[tiab] OR Malignant Fibrous Histiocytoma*[tiab] OR Leiomyosarcoma*[tiab] OR Liposarcoma*[tiab] OR Lymphangiosarcoma*[tiab] OR Mesodermal Mixed[tiab] OR Myosarcoma*[tiab] OR Rhabdomyosarcoma*[tiab] OR Myxosarcoma*[tiab] OR Osteosarcoma*[tiab] OR Ewing Sarcoma*[tiab] OR Phyllodes[tiab] OR Gastrointestinal Stromal[tiab])) AND ((((“Delayed Diagnosis”[Mesh])) OR (“Diagnostic Errors”[Mesh:noexp]) OR (“Early Diagnosis”[Mesh]) OR (((Delay*[tiab] OR late[tiab] OR Waiting time*[tiab]) AND (diagnos*[tiab] OR Referral*[tiab] OR Referal*[tiab] OR Journey*[tiab])))))) NOT “Case Reports”[Publication Type])) NOT ((((((“Child”[Mesh]) OR “Infant”[Mesh])) OR Adolescent[mesh])) NOT “Adult”[Mesh])))))

Supplementary material B

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5/discussion
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Discussion
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6 and onwards tables 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6 onwards
Synthesis of results	21	Present the main results of the review.	6 onwards
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Discussion
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			n/a
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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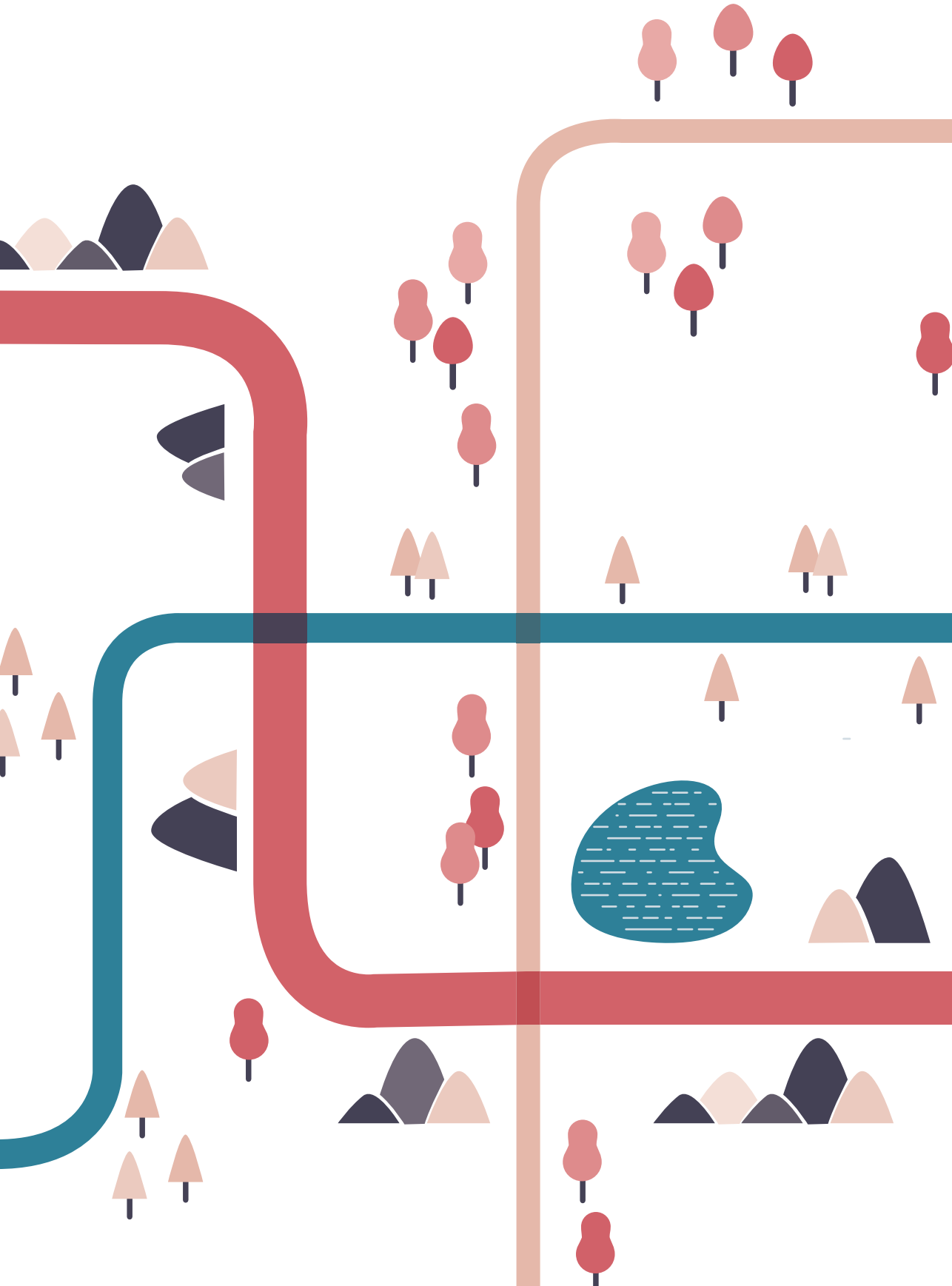

CHAPTER 3

The route to diagnosis of sarcoma patients: results from an interview study in the Netherlands and the United Kingdom: a qualitative study

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Abstract

Introduction

Sarcomas are rare tumours. Early diagnosis is challenging, but important for local control and potentially survival and quality of life(QoL). We investigated (1)the route to diagnosis (RtD) experienced by sarcoma patients, including factors contributing to the length of the RtD from patients' perspective; (2)the impact of the RtD on QoL and care satisfaction; and (3)differences in aims 1-2 between English and Dutch patients.

Methods

Fifteen sarcoma patients from The Royal Marsden Hospital, United Kingdom, and Radboud University Medical Centre, The Netherlands, were interviewed, exploring RtD experiences. Interviews were analysed according to qualitative content analysis.

Results

The main themes were: patient interval, diagnostic interval, reflection on the RtD and recommendations for improvement. Patient interval was long if symptoms were attributed as benign, did not interfere with daily life or were expected to cease. An incorrect working diagnosis, ineffective process of additional investigations, long referral times and lack of a lead clinician lengthened the diagnostic interval. Long waiting times, false reassurance and inadequate information provision led to dissatisfaction and a high emotional burden. Factors for improvement included increasing awareness of patients and healthcare providers, empowering patients, and having a lead clinician.

Conclusion

The RtD of sarcoma patients is complex. Increasing awareness of patients and healthcare providers may contribute to shorten the RtD.

Introduction

Sarcomas are mesenchymal tumours which comprise more than 70 histological subtypes. They are heterogeneous in terms of age of onset, presentation, anatomic location, speed of progression and clinical outcome. Approximately 85% of sarcomas originate in soft tissue, the remainder in bone. Sarcomas have an estimated incidence averaging 4-5 per 100,000 per year in Europe[4] and are a so-called rare cancer. Patients with rare cancers have a higher mortality rate than those with common cancers because of delays in accurate diagnosis, suboptimal or inadequate treatment, fewer opportunities to participate in clinical trials and less availability of novel agents[5].

Early and adequate diagnosis of sarcoma is challenging due to the heterogeneity in presentation and histology, but is important for local control, and potentially (health-related) quality of life ((HR)QoL) and survival, as seen in other cancer diagnoses[6-11]. Different histological sarcoma subtypes vary in biological behaviour; some aggressive sarcomas cause severe symptoms at an early stage, leading to an early presentation and potentially faster diagnosis, but with a worse outcome than sarcomas that grow slow, causing symptoms with a long total interval. The total interval is the time between first symptoms and (preferably histological) diagnosis (Fig 1)[3].

Apart from cancer characteristics, patient and healthcare factors can be of influence on the length of the total interval[3, 12]. Until now, contradictory results have been found for the influence of patient characteristics[13]; data on comparison of healthcare systems is scarce for sarcomas. The healthcare system of The Netherlands(NL) and United Kingdom(UK) are comparable but differ regarding sarcoma referral pathways.

Patients in both countries have access to health services via a publicly funded healthcare system[14] and generally the general practitioner (GP) is the first healthcare provider(HCP) to be consulted, who refers to secondary or tertiary centres if appropriate. In the UK a minority of patients (11%) is privately insured giving them access to private hospitals via self-referrals, in NL patients may, if they can afford it, use certain diagnostic services provided in private clinics. Sarcoma care has been centralized in the UK, and although bone sarcoma centres exist in NL, care for patients with soft tissue sarcomas has not formally been centralized.

The aim of this study is to investigate (1)the route to diagnosis(RtD) experienced by sarcoma patients, including factors contributing to the length of the total interval from the perspective of a patient; (2)the impact of the RtD length on QoL and care satisfaction; and (3)differences in aims 1-2 between English and Dutch patients.

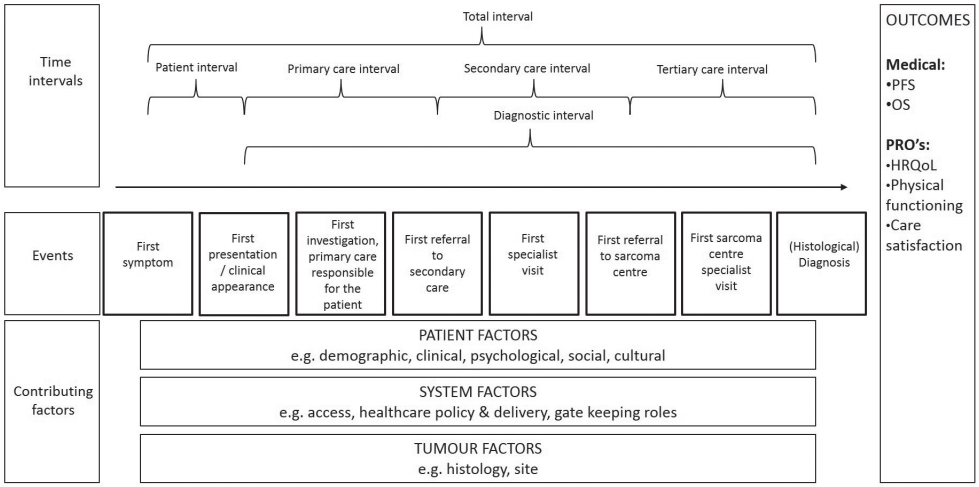

Fig 1: Definitions of the route to diagnosis for sarcoma patients

This fig was adapted from Olesen et al and Walter et al[1-3]

- Patient interval: from the date the patient first noticed a sarcoma related symptom until the first presentation to a doctor with this symptom;
  - Appraisal: from noticing a sarcoma related symptom to deciding to seek the help of a healthcare provider (HCP);
  - Help-seeking: from making the decision to consult a HCP until the actual appointment;
- Diagnostic interval: from first presentation to a doctor until diagnosis;
  - Primary care interval: from first presentation to a general practitioner (GP) until first referral to secondary (if applicable) or tertiary care, in this study the sarcoma centre (in which referral is the time point at which there is a transfer of responsibility from one HCP to another);
  - Secondary care interval: from referral to secondary care specialist until referral to tertiary care specialist;
  - Tertiary care interval: from referral to tertiary care specialist (sarcoma centre) until date of histological diagnosis;
- Total interval: from first symptom until histological diagnosis.

Methods

Conceptual framework

To study the RtD, a framework for research with clear definitions is needed. In this study we combined the widely used models of Olesen *et al* and Walter *et al*, as shown in Fig 1[1-3]. The combined model identifies a patient interval, which can be divided between the process of appraisal and help-seeking, and a diagnostic interval, which can be divided into a primary, secondary, and tertiary care interval, the latter was added to fit the sarcoma referral pathway. The treatment interval was left out, as it is out of the scope of this study. The events marking the beginning and end of each interval can be found in Fig

1. The length of each interval can be influenced by patient, system and tumour factors, which will eventually influence clinical and patient-reported outcomes, represented by the outcomes column to the right. This theoretical framework will be used to describe patients' experience of the sarcoma RtD.

Study design and patient recruitment

We conducted semi-structured interviews between March and November 2017. Patients were eligible if they were (1)≥18 years; (2)diagnosed within the past 4 months in Radboud University Medical Centre (Radboudumc), NL, or the Royal Marsden NHS Foundation Trust, UK, with histological proven sarcoma and (3)could communicate in Dutch or English, respectively. Patients with significant cognitive impairment or mental health problems, as determined by their HCP, were excluded.

At both sites, eligible patients were identified by their HCP or a member of the research team(VS) and supplied with an information letter. VS then contacted the patients to answer remaining questions and, if agreeing to participate, to set a time for the interview. All participants provided written informed consent before the interviews. Participants completed demographic and clinical questions prior to the interview. RtD, QoL, and care satisfaction were subjects within the interview, and not subject of the questionnaire.

In the UK the study was deemed exempt from full review and approval by a research ethics committee (Committee for Clinical Research, Royal Marsden NHS Foundation Trust), but was approved by the service evaluation committee of the Royal Marsden NHS Foundation Trust(SE669). In NL the study was approved by the medical ethical committee of the Radboudumc(2017-3229).

Data collection, analysis and reporting

Patients completed a short questionnaire on sociodemographic data and dates of referral. Date of referral to the sarcoma centre and the date of histological diagnosis was confirmed from medical records.

Semi-structured interviews were conducted by one member of the research team at both sites(VS), the interview schedule is provided in appendix 1. VS had no clinical relationship with the participants or the treating physician. The interviews were conducted at the hospital. Topics and questions were based on clinical experience and literature review[13, 15-17], whilst emerging questions from interviews were discussed in the following interviews. The interviews were recorded and transcribed verbatim and anonymously. Data analysis was conducted by two coders(VS and OH) using ATLAS.ti 8.0. Data was analysed according to qualitative content analyses and were ordered into relevant code terms, and then categorised into themes by two researchers(VS and OH). Data answering

the first research question was organized according to our conceptual framework (directed approach)[18]. The second and third research question were answered by conventional content analyses, in which coding categories are derived directly from the data[18]. After analysing the data independently, the coders discussed and redefined until they reached consensus. Saturation was reached when no new themes were identified. The consolidated criteria for reporting qualitative research(COREQ) were used. Appendix 2 provides an overview of translated quotes.

Results

Participants

Seven Dutch and eight English patients with a total interval varying between 10-145 weeks participated. All invited patients gave informed consent and participated in the study. Both patient and diagnostic interval contributed to a prolonged total interval: though the median patient interval was 4 weeks, it ranged from 0-119 weeks; the median diagnostic interval was 18 weeks with a range of 3-140 weeks. More details on these intervals and socio-demographic and clinical characteristics of the patients are presented in Table 1. The study participants reflect the heterogeneity of the sarcoma population.

Themes

The first research question is answered by the first two themes, which are organized according to our conceptual framework. The other two main themes, 'reflection of diagnostic pathway' and 'recommendations for improvement of the diagnostic pathway' give an answer to the second aim of this study, to describe the impact of RtD length on QoL and care satisfaction of sarcoma patients. The third research question is accounted for under all themes. Fig 2 shows a schematic representation of our main findings, quotes to support our results can be found in Table 2.

Table 1: Patient and diagnostic interval characteristics

Patient †	Age	Sex	Diagnosis and site	Total interval (weeks)	Patient interval (weeks)	Diagnostic interval (weeks)	Primary care interval (weeks)	Number of visits / number of doctors seen in primary care	Secondary care interval (weeks)	Number of visits / number of doctors seen in secondary care	Tertiary care interval (weeks)	Number of visits / number of doctors seen in tertiary care
				Median: 24	Median: 4	Median: 18						
1	24	M	High-grade osteosarcoma of the radius	26	3	23	6	2 / 1	13	2 / 1	4	2 / 1
2	68	M	High grade peripheral nerve sheath sarcoma of upper leg	49	16	33	1	2 / 1	27	9 / 6	5	1 / 1
3	40	F	Solitary fibrous tumour pelvis with multiple metastases	32	0	32	23	2 / 2	7	6 / 4	2	3 / 2
4	65	F	Leiomyosarcoma uterus with liver metastases	10	3	7	2	2 / 1	6	6 / 2	0	n.a.
5	41	F	High grade osteosarcoma femur	22	11	11	0	1 / 1	1	2 / 1	10	3 / 1
6	54	F	Solitary fibrous tumour wrist	137	119	18	4	2 / 1	8	2 / 1	6	2 / 1
7	18	M	Ewing sarcoma cerebellum	15	12	3	1	2 / 1	0	1 / 1	2	2 / 1
8	69	F	Solitary fibrous tumour groin	13	0	13	5	2 / 1	9	2 / 2	0	n.a.
9	85	F	Leiomyosarcoma colon transversum with possible lung lesions	22	9	13	5	2 / 2	9	3 / 1	0	n.a.
10	51	F	Low grade endometrial stromal sarcoma uterus	99	57	42	6	2 / 1	36	5 / 1	0	n.a.

Table 1: Continued

Patient †	Age	Sex	Diagnosis and site	Total interval (weeks)	Patient interval (weeks)	Diagnostic interval (weeks)	Primary care interval (weeks)	Number of visits / number of doctors seen in primary care	Secondary care interval (weeks)	Number of visits / number of doctors seen in secondary care	Tertiary care interval (weeks)	Number of visits / number of doctors seen in tertiary care
				Median: 24	**Median: 4**	**Median: 18**						
11	50	M	Extra-osseous Ewing sarcoma thorax	64	4	59	0	1 / 1	56	5 / 3	3	2 / 1
12	48	F	Extra -osseous Ewing like sarcoma thorax	145	4	140	137	6 / 2	0	2 / 1	3	3 / 2
13	61	M	Retroperitoneal dedifferentiated liposarcoma	24	4	20	14	3 / 3	2	1 / 1	4	2 / 2
14	56	F	Undifferentiated pleomorphic sarcoma m. erector spinae	16	1	16	13	3 / 1	0‡	n.a.	3	2 / 2
15	69	M	Well differentiated retroperitoneal liposarcoma	10	1	8	0	1 / 1	7	2 / 1	1	2 / 1

†Patients 1-7 were Dutch, patients 8-15 were English. ‡Direct referral from GP to sarcoma centre.

Theme 1: Patient interval

Subtheme: Appraisal

Category 1: factors contributing to short interval: opposite to category 2.

Category 2: factors contributing to long interval: (1) alternative explanation for symptoms; (2) no interference with daily life; (3) expectation to cease over time.

Subtheme: Help-seeking

Category 1: factors contributing to short interval: (1) interference with daily life; (2) prolongation or worsening of symptoms; (3) little waiting time for appointments.

Category 2: factors contributing to long interval: opposite to category 1.

Theme 2: Diagnostic interval

Subtheme: Diagnostic phase

Category 1: factors contributing to short interval: (1) follow-up of investigations until diagnosis has been made; (2) fast referrals; (3) having a head clinician.

Category 2: factors contributing to long interval: (1) wrong working diagnosis with lack of follow-up; (2) ineffective process of additional investigations; (3) long referral times; (4) no adjustment of working diagnosis; (5) long time to get histological diagnosis; (6) lack of a head clinician.

Subtheme: Effect of centralisation

(1)Time consuming; (2) costly; (3) not a barrier to receive care.

Theme 3: Reflection on diagnostic pathway

Subtheme: Care satisfaction

Category 1: factors contributing to satisfaction: (1) HCPs did what they said they would do; (2) information provision was satisfactory; (3) patients were taken serious.

Category 2: factors contributing to dissatisfaction: (1) long waiting times; (2) symptoms being ignored; (3) falsely reassurance; (4) information provision inadequate.

Subtheme: Impact of receiving the diagnosis

(1) Shock; (2) worried about loved ones.

Subtheme: Impact of delay on:

Category 1: medical outcomes: most thought there was no relationship between medical outcome and length of diagnostic interval.

Category 2: patient reported outcomes: high emotional burden of long diagnostic interval.

Theme 4: Recommendations for improvement of the diagnostic pathway

(1) Awareness of patient and HCP; (2) empowerment of patients; (3) having a lead clinician.

Figure 2: Schematic representation of main findings

Table 2: Quotes

Theme	Subtheme	Quote
Patient interval	Appraisal	*'Initially we thought it was a, like a bug bite' (male, #11).*
		'I stopped doing sport and waited without having any concerns' (male, #1).
		'I was made this appointment at a back-specialist clinic and again he [a physiotherapist] completely examined me and he quite 100% told me that you have got a class-3 classic sciatica. He just said, keep taking your medication, you're on the best medication that you can get. [...] Well, with that I then continued' (male, #13).
	Help-seeking	*'I waited until it started to affect my style of life. I do a manual job [...]. So, I carried on until basically it started to affect, you know, my daily work' (male, #13).*
		'Then last year around about Christmas time we noticed it getting much bigger and taking on a red, a reddish, sort of like a bruise. So, and it started becoming quite can I say noticeable. I couldn't put my arm down properly and couldn't sleep on that side. And it did start giving me pain' (male, #11).
		'At that moment the pain became worse, [...]it really hurt in the buttocks and the back of my legs. I thought, this really can't be any good' (female, #4).
		'What made me decide to [make an appointment]? Because it wasn't getting better. More frequent I expect and a lot of...soreness in the lower abdomen.' (female, #9).
		'I was just getting scared because the pain, the pressure in the ribs, it wasn't going away. And I did have coughs and things like that, then they went away, then a lot of mucus then they went away. But it just, you know, something wasn't right' (female, #12).
Diagnostic interval	Diagnostic phase	*'" It's a hematoma because you've obviously pulled a muscle and you know you've pulled a muscle and it looks much like a hematoma" they said. [...] You don't like to dreadfulize, you don't like to think what ifs. I had pulled muscles in the past and they have been painful, and I have had problems with back muscles in the past through dangerous sports, so I just assumed at the time that they were correct, it was a hematoma.' (female, #14)*
		'Waiting for 6 weeks for an MRI is actually extremely long I think. If I would have been aware that it might not be benign, I would not have agreed with that. But I wasn't, so I just went on a holiday, spent the entire day in the sun and drank alcohol. I was extremely, extremely, extremely tired' (male, #1).
		'The referral for that second opinion at the sarcoma centre had to go through the GP' (male, #2).
		'The GP never referred me to get a CAT-scan because they [the GP] said I was fit, healthy, non-smoker, never had any family condition or history of anything bad. I had no pre-existing conditions of anything and I took no medication at all, so they said that there was no reason for a CAT-scan. [...] So, they stopped there and every time I went back they thought it was musculoskeletal' (female, #12).
		'[...] and then a biopsy 3 times. They punctured 3 times, so they would have enough, but they hadn't because it turned out they were still in doubt between a chondrosarcoma and an osteosarcoma. After that I got a biopsy under general anaesthesia and that showed it was an osteosarcoma, but low grade. [...] Then I had an operation, which went well, but they found other, more aggressive, cells, which is why I had to come here [medical oncology department] eventually' (male, #1).
		'They had to send the tissue sample to another hospital because they weren't sure, I think that's when they pushed back the appointment and then when they had it confirmed at the hospital they brought it [the appointment] forward' (female, #10).
		'But it wasn't the same doctor. The first time I saw, I had seen my own doctor but the second time it was another doctor' (male, #13)

Table 2: Continued

Theme	Subtheme	Quote
		'So, my GP looked and investigated me but did not know what it was, so he sent me for an ultrasound that same afternoon' (female, #5).
		'The doctor said: "if I had not seen you on Sunday and I had not seen the difference between Sunday and Friday, then I probably would not even have referred you to the hospital"' (male, #7).
	Effect of centralisation	*'Yes, I had to get used to the travel distance. […] The travel costs, it was my savings I used. You can ask something back from the insurance company, that is nice, but in the beginning it did cost a bit more money' (male, #1).*
Reflection on diagnostic pathway	Care satisfaction	*'[Getting the diagnosis took] roughly 4 months. If I look back at those dates, perhaps two or three weeks might have been saved by a referral being sent on as soon as I was seen as opposed to me phoning up to see if that had gone. So, apart from that I can't really, fault anybody or the process of the system.' (female, #8).*
		'I'm very angry. I'm not saying that they ... [pause], it could've been done better. [..] For me to get where I am now I don't think it would've [been necessary]' (male, #13).
		'Well I suppose if I had been a private patient, I would have been seen and all this would have happened maybe half the time or maybe less. So on looking at the NHS I'm being realistic and thinking they have done the best they can.' (female, #8).
		'But...it's a case, when they're all available. They are very, very pushed. I think there's too many patients in our practice anyway.' (female, #9).
	Impact of receiving the diagnosis	*'I entered the room and he said: "I have not got good news for you". I then thought: "wow". It was like a rollercoaster. I had gone alone. I was startled, absolutely. No, I really did not see it coming. It came out of nowhere.' (male, #1).*
		'Everybody said the chances of it being anything suspicious were absolutely minute, so I had no reason to feel concerned at all. To be told...actually that's not what you thought it was. Alright, okay where do we go now? [..] I was just so surprised after everything being..."yes, yes everything looks good, everything looks good". Then bang... [..] They don't know how to express too much sympathy.' (female, #10)
	Impact of delay on medical outcomes and quality of life	*'Yes, I understand it does influence my prognosis' (male, #2).*
		'It was difficult from the moment of the result at the hospital until the scans. Especially after the scans I was wondering: "is it somewhere else, how bad is it?" I thought I was dying.' (male, #1).
		'I suppose the most difficult part was not knowing, or waiting, knowing that in all these investigations would obviously help towards the diagnosis and just waiting and not knowing. [..] But never the less I just got on with life.' (female, #8).
Advice Recommendations for improvement of the diagnostic pathway		*'Be persistent for what you want [to know]. If you don't know [what's going on] and you want to know then you just have to be persistent about it' (female, #9).*
		'Everything could have gone faster if people had been more aware that this could be sarcoma' (male, #1).
		'A patient should at the moment of getting complaints of peeing or whatever take it seriously straight away' (female, #3).
		'The key is to start with your general practitioner' (female, #5).
		'Possibly my doctor himself should have pushed slightly more rather than saying: yes, that's fine, you can leave it until after your holidays, [the GP] should've possibly said: "no, let's fix it beforehand"' (female, #14).

Theme 1: Patient interval: appraisal and help-seeking

Appraisal

Three factors were identified that contributed to a long phase of appraisal. First, many patients had an alternative, benign explanation for their symptoms. In some cases, this alternative explanation was not something a patient would need to seek the help of a HCP for (e.g. a bug bite), while in other cases the symptom was normalised by the patient as being part of life (e.g. old age). Second, if the symptoms did not interfere with daily life, most patients did not feel the urge to seek help. The process of help-seeking was often delayed further due to other life priorities (e.g. a holiday), stopping with activities that became difficult due to symptoms (e.g. gardening), and treatment from a paramedical HCP which decreased complaints temporarily. Third, many patients expected their complaint to cease by itself.

Help-seeking

The main trigger of help-seeking was interference of the symptoms with daily life. If symptoms lasted or became worse, this was an extra reason to seek help. There were no delays in making an appointment with an HCP. There were no remarkable differences in the patient interval between NL or the UK.

Theme 2: Diagnostic interval: diagnostic phase and effect of centralisation

Diagnostic phase

Once the patient seeks help from a HCP, he or she enters the diagnostic phase. This phase was found to be lengthened by six factors, which could send patients back to the process of appraisal.

First, the HCP often had a "working diagnosis" for which wait-and-see management was legitimate. However, a lack of follow-up to ensure resolution of symptoms attributed to a long diagnostic phase.

Second, the process of additional investigations was prolonged: (1)performing investigations was often postponed, (2)passive waiting time for imaging studies and biopsies, (3)long time between investigations and receiving results, and (4)absence of subsequent investigations if results were inconclusive or (false) negative.

Third, referrals took a long time due to: (1)referrals to the wrong specialist, (2)second opinions needed to go through the GP, or (3)long waiting times for an appointment at the sarcoma centre.

Fourth, if the course of disease progression was different than expected, often the working diagnosis was not adjusted, and no new investigations were ordered.

Fifth, if a biopsy was performed it took a long time to get a diagnosis due to the rarity of the disease, heterogeneity and difficulty to diagnose, more tissue needed or necessity to send the material to a sarcoma pathologist.

Sixth, the lack of a lead clinician lengthened the diagnostic process, e.g. when a patient was repeatedly referred to a different specialist at another hospital, or if follow-up consultations did not take place with the same doctor. This was more evident in English than in Dutch interviews, whereas the other causes were mentioned by both groups of patients.

Similarly, the reverse of these factors led to a short diagnostic interval. Especially investigations done within a short time frame, smooth referrals, awareness of the patient that something was wrong and having one lead clinician facilitated fast diagnosis.

Effect of centralisation

Many patients acknowledged centralisation of sarcoma care had been difficult in terms of travel distance, arranging transport, the necessity to take longer time off from work, and paying travel expenses from their own savings, especially in the UK. Although travelling to a sarcoma centre or being admitted away from home felt as an effort, it was not a barrier for them to visit a sarcoma centre as they believed they received better care.

Theme 3: Reflection on diagnostic pathway: satisfaction with care and impact of delay

Care satisfaction

Patients were satisfied about the received care if (1)HCPs kept their promises, (2) information provision was satisfactory, and (3)patients felt they were taken seriously. The absolute length of the diagnostic interval was mostly not of influence on the level of satisfaction with care, but the (subjectively) experienced length was important.

Patients were unsatisfied if (1)there were long waiting times, (2)they felt their symptoms were ignored, (3)they were falsely reassured, and (4)information provision was inadequate. In the UK patients felt that their doctors were busy, and the system was pushed, therefore not faulting their doctor but the system they needed to work in. They thought this caused GP's to be less proactiveand thought waiting times were longer due to the National Health Service(NHS) and would have been shorter if they were privately insured. This was not applicable to Dutch patients.

Impact of receiving the diagnosis

Most patients who experienced a long diagnostic interval felt shocked when they received the diagnosis. Those who experienced a short diagnostic interval were more concerned about their loved ones than themselves.

Impact of delay on medical outcomes and quality of life

Only one patient thought a long diagnostic interval influenced his clinical outcomes. However, the emotional burden with feelings of anxiety, fear of dying, and anger was mentioned by most patients. The impact of a long interval on quality of life was largest when patients had not expected a malignant diagnosis. They also experienced the period in which they knew they had a malignancy but had to wait for the definite diagnosis as difficult.

Theme 4: Recommendations for improvement of the diagnostic pathway

Patients gave advice regarding improvements of the diagnostic pathway. First, awareness of both the patient and HCP was described as a requisite for an efficient diagnostic pathway. Awareness leads to investigations being done in a shorter time frame due to persistence of patients or recognized necessity for investigations by the HCP. Second, patients indicated they can be empowered by receiving copies of referral letters. Third, each patient should have a lead clinician, who tracks results of investigations until a diagnosis has been made. Many patients emphasized the importance of the role of the gatekeeper, most often the GP. If the gatekeeper ordered the right investigations or referred them to the correct specialist most RtD's went smoothly. If the gatekeeper reassured them, referred to the wrong specialist, or postponed investigations or referrals, then patients lingered for a long time. These recommendations were the same among Dutch and English patients.

Discussion

This study investigated the RtD as experienced by sarcoma patients, its effect on QoL and care satisfaction and differences between English and Dutch patients. We found the RtD to be variable and many sarcoma patients encounter difficulties during the process. The total interval of our patients varied from 10 to 145 weeks, this large variability is concurrent with the literature[13].

Our study identified four main themes: patient interval, diagnostic interval, reflection on diagnostic pathway and recommendations for improvement of the diagnostic pathway; fig 2 shows a schematic summary of our main findings.

Factors influencing the length of the patient interval were alternative explanations for symptoms, interference with daily life, expectations about prolongation of symptoms and waiting time for appointments. The diagnostic interval was lengthened if the working diagnosis was inaccurate or not adjusted, the process of investigations and receiving their results was inefficient, there was a lack of a head clinician, or there were long referral times. These associations are in concurrence with existent cancer literature, which has shown that key concepts for length of patient and diagnostic interval were recognition and interpretation of symptoms, the impact on everyday life by symptoms, experiences of generalist health care, entry into secondary care, repeated cycles of healthcare seeking and appraisal without resolution and lack of follow-up of persisting symptoms[15-17, 19, 20]. As shown in our study, the role of the GP or subsequent lead clinician is important for referral times and promptness of successive additional investigations.

Sarcoma care is centralized in sarcoma expert centres in many countries, it is generally accepted that this improves diagnosis and subsequent treatment[4, 5]. We explored the effect of centralisation on patients' experiences of the diagnostic pathway. For nearly all included patients, travelling to a sarcoma centre was time consuming and costly, but not withstanding them from going there to receive the best possible care.

Although the diagnostic interval was perceived more negative by English patients, care satisfaction was equal amongst Dutch and English participants. An interesting finding is that the absolute duration of the diagnostic interval was not of influence on care satisfaction as reported by our participants. They were unsatisfied with passive waiting time, being ignored or falsely reassured, and if information provision was inadequate. The reverse of these factors improved their level of care satisfaction. To the best of our knowledge, the influence of RtD on care satisfaction has not been measured. However, there is a lot of literature and policy reports measuring RtD length including anecdotal evidence that the large number of prolonged time to diagnosis will lead to lower care satisfaction[13, 21, 22]. The European patient advocacy group (SPAEN) has written a position paper in which the first priority challenge is earlier accurate diagnosis[23]. This underlines the importance of a fast RtD for patients. Delays to diagnosis have also been shown to be the main cause of sarcoma litigation[24, 25]. General cancer literature has shown contradictory results about the relation between care satisfaction and experienced RtD; a qualitative study with 26 patients with anal cancer showed most patients were satisfied with received care, unless they experienced passive waiting time[26]. However, another study in 353 women with gynaecological cancer reported a longer diagnostic interval led to lower care satisfaction[10], and a study in 904 cancer patients showed patients had less confidence in GPs after being diagnosed with a doctor delay [27]. Upon receiving the diagnosis patients with a long interval felt shocked, those with a shorter interval were mainly worried about their family.

Research about the effect of the length of total on clinical and patient-reported outcomes is mostly retrospective and shows contradictory results[13]. However, a long total interval could cause significant psychological morbidity[9]. Participants in our study confirm that waiting time causes psychological distress. Yet, only one patient considered his delayed diagnosis to influence his clinical outcome. This is an additional rationale to investigate the effect of the length of diagnostic interval on both clinical as well as patient-reported outcomes.

The fourth theme, recommendation for improvement of the diagnostic pathway, provided us with information consistent with existing cancer literature but now from a patients' perspective: the main recommendations were to increase awareness amongst patients and HCPs, to empower patients, and to have one lead clinician[12, 15, 20].

This study has given us insight in the patients' perspective of the diagnostic pathway. Nevertheless, several limitations should be considered. First, although qualitative study methods are ideal to gain insight in what is important and why, this is a descriptive study and results can therefore not be generalized to all sarcoma patients. The RtD is influenced by healthcare systems, culture and organization of care and therefore these results cannot be generalized to sarcoma patients outside NL or the UK. In our analyses, the same factors facilitating and prolonging time to diagnosis emerged from all interviews. In that respect, we concluded we reached data saturation and did not add any more participants. However, due to the heterogeneity of the disease, depending on subtype and location, patients will encounter many different specialist in the RtD. As shown in this study, this results in many different pathways and we cannot say we explored all possible cases. Second, one of the aims of our study was to examine the effect of the RtD on QoL. However, the impact on QoL was not a main issue in our interviews. To investigate whether QoL is truly not impacted by length of the total interval, quantitative research is needed. Third, we left the treatment interval out of the scope of our study. Outcomes may be influenced by this time interval, and some patients had just heard their diagnosis whereas others had already started treatment, which may have influenced their responses. Fourth, patient interval dates were patient-reported and therefore possibly inaccurate. To limit recall bias, we included and interviewed patients within four months after diagnosis, in our clinical experience patients remember many details about their RtD, we therefore think this bias is limited.

Until now, the conceptual framework used to describe the RtD was a theoretical model representing methodological recommendations. Our study described the patient experience of sarcoma diagnosis and for the first time confirms that this patient experience fits the model. This is an important finding, because understanding the RtD from both the patient and clinical perspective is necessary to improve the diagnostic pathway.

Our study confirms the research model as presented in fig 1 is useful for sarcoma patients and can be used in future research to report uniformly on the subject. The fig could be given more detail specifically for sarcoma patients, e.g. contributing events could be complemented with patient awareness and empowerment for patient factors, direct access to investigations and having a lead clinician are important system factors and care satisfaction is influenced by passive waiting times. However, to make these findings more robust and to study the effect of total interval on outcomes, more research is needed. This qualitative study was used to identify factors important to patients, to use in our design of a large quantitative and prospective longitudinal study, currently a trial in progress (the 'QUEST' study, NCT03441906). This study will allow us to quantify total interval and its components, provide insight in factors contributing to its length, and study the relationship between its length and clinical as well as patient-reported outcomes. If the sample is large enough, we may be able to distinguish these features for specific sarcoma subtypes. Hopefully it will allow us to give a more detailed insight in what is specific in the RtD for sarcoma patients, compared to other malignancies. The present study has contributed to understanding patients' experiences during the diagnostic process and has enabled us to design a study in which the patients' perspectives are involved.

Conclusion

This study confirmed RtD for sarcoma patients is variable and found several patient and system factors influencing its length for English and Dutch patients, and described its effect on care satisfaction. The total interval could be reduced by increasing awareness amongst patients and HCPs, having an efficient pathway for investigations and referrals and working with a lead clinician. Centralisation of care is costly and time consuming, but not a barrier for receiving care. The patients' experience of the RtD could be improved by reducing passive waiting time and providing adequate information. Quantitative research is needed to confirm these findings and study the impact of RtD on clinical and patient-reported outcomes.

Acknowledgements

The authors thank all patients who were willing to participate in this study.

S1 Appendix 1 interview schedule

Introductory question

Can you briefly give me the outlines of what happened when you experienced your first symptoms until the moment the diagnosis of sarcoma was made?

Core questions

If you think back at the period in which you first noticed your symptoms, what was your explanation for having those symptoms?

If appropriate: What do you think delayed you going to a doctor?

What made you go to the doctor (in the end), and what happened when you did?

During the diagnostic pathway, did finance or travel distance, including taking days off work etc, play a role in the decisions you made? How?

How did you feel about the diagnosis itself?

Looking back at the entire pathway, which period do you feel was the most difficult in a psychological way? Why?

What do you think the effect of the length of the diagnostic pathway is / has been?

Looking back, would you have done anything differently?

Are you satisfied with the care you have received? Why (not)?

Closing question

Have you got recommendations on how to improve the diagnostic pathway?

S2 Appendix 2 translated quotes

Translated quote	Original quote
'I actually had some problems with peeing for some time. You just put it aside as being: 'you get older, so you may need to go to the bathroom more quickly or just drink more' (female, #3).	Eigenlijk had ik bepaalde klachten met plassen al langer. Alleen dat zet je dan weg als zijnde: je wordt ook ouder, dus misschien moet je sneller naar de wc of je drinkt gewoon wat meer.
'I stopped doing sport and waited without having any concerns' (male, #1).	Ik ben gestopt met sporten en gewoon even afgewacht zonder enige onrust.
'Waiting for 6 weeks for an MRI is actually extremely long I think. If I would have been aware that it might not be benign, I would not have agreed with that. But I wasn't, so I just went on a holiday.' (male, #1).	6 weken wachten op een MRI is ook eigenlijk extreem lang vind ik. Als ik mezelf er al van bewust was dat het niet goed zou kunnen zijn, dan was ik daar niet akkoord mee gegaan. Dat was ik dus niet, ik ben gewoon op vakantie geweest.
'The referral for that second opinion at the sarcoma centre had to go through the GP' (male, #2).	Die verwijzing voor die second opinion hier naar het Radboud moest via de huisarts.
'They biopsied 3 times so they would have enough, but they hadn't because it turned out they were still in doubt between a chondrosarcoma and an osteosarcoma. After that I got a biopsy under general anaesthesia and that showed it was an osteosarcoma, but low grade. [...] Then I had an operation, which went well, but they found other, more aggressive, cells, which is why I had to come here eventually' (male, #1).	'Ze deden dat [biopteren] extra 3 keer want dan zouden ze genoeg hebben, maar ook dat was niet genoeg, omdat ze toen aan het twijfelen waren tussen een chondrosarcoom en een osteosarcoom. Daarna kreeg ik een biopt onder narcose en die liet zien dat het een osteosarcoom was, maar laaggradig. […]De operatie gedaan, dat was wel gelukkig goed gegaan, maar dan toch andere agressieve cellen gevonden, waardoor ik toch hier in het traject ben beland.
'That MRI-centre is nearby and I just went there and said: "I want you to make an MRI of my leg". They do that if you pay for it yourself' (male, #2).	Dat MRI-centrum zit in Elst en daar ben ik gewoon langsgegaan en gezegd: 'ik wil dat er een MRI van mijn been gemaakt wordt'. Dat kan als je het zelf betaalt.
'So, my GP looked and investigated me but did not know what it was, so he sent me for an ultrasound that same afternoon' (female, #5).	Dus hij heeft gekeken en onderzocht en vond het eigenlijk ook maar, ja, kon het ook niet thuis brengen, dus hij heeft me eigenlijk gelijk 's middags voor een echo gestuurd
'The doctor said: "if I had not seen you on Sunday and I had not seen the difference between Sunday and Friday, then I probably would not even have referred you to the hospital"' (male, #7).	De dokter heeft ook zelf gezegd van: had ik jou die zondag niet gezien en het verschil niet gezien tussen zondag en vrijdag, dan had ik je waarschijnlijk vrijdag niet eens doorgestuurd naar het ziekenhuis.
'Yes, I had to get used to the travel distance. […] The travel costs, it was my savings I used. You can ask something back from the insurance company, that is nice, but in the beginning it did cost a bit more money' (male, #1).	Ja, die reisafstand was in het begin wel even wennen. […]Het is een buffertje wat je op gaat maken voor ons. Je kunt ook een gedeelte terugvragen bij CZ, dus dat is ook wel fijn, maar op dat moment kost het wel wat meer geld.
'I entered the room and he said: "I have not got good news for you". I then thought: "wow". It was like a rollercoaster. I had gone alone. I was startled, absolutely. No, I really did not see it coming. It came out of nowhere.' (male, #1).	Ik kwam binnen en hij zei het al gelijk toen ik binnen was: 'ik heb geen goed nieuws voor je'. Toen was ik echt van: wow. Dan kom je in het circus, eigenlijk een achtbaan. Ik was ook alleen gegaan. Het was wel schrikken, absoluut.
'Yes, I understand it does influence my prognosis' (male, #2).	Ja, dat begrijp ik volgens mij dat het mijn prognose beïnvloedt.
'It was difficult from the moment of the result at the hospital until the scans. Especially after the scans I was wondering: "is it somewhere else, how bad is it?" I thought I was dying.' (male, #1).	Het was gewoon zwaar van het moment in het ziekenhuis bij de uitslag tot na de scans. Vooral na die scans dat jij je afvraagt: zit het nog ergens anders, hoe ernstig is het. Ik dacht wel dat ik doodging.
'Everything could have gone faster if people had been more aware that this could be sarcoma' (male, #1).	Alles had sneller kunnen gaan als mensen zich meer bewust zouden zijn dat dit een sarcoom kan zijn.
'The key is to start with your general practitioner' (female, #5).	De kern is toch dat je bij je huisarts begint.

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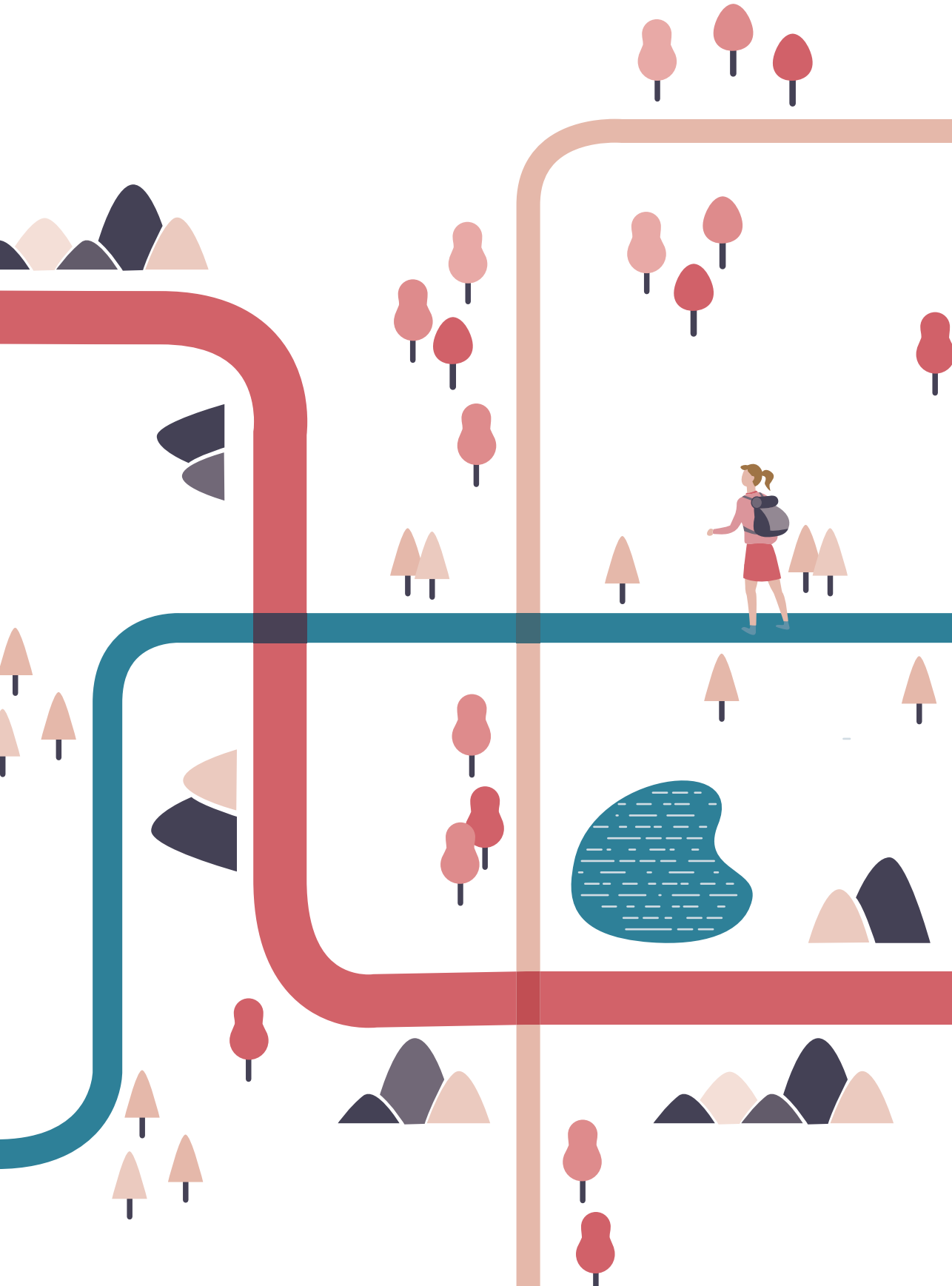

CHAPTER 4

Patient and diagnostic intervals of sarcoma survivors: results from the SURVSARC study

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Abstract

Background

Sarcoma patients are hypothesized to experience a prolonged route to cancer diagnosis. This route, the total interval, can be divided into a patient (time from symptom to doctor consultation) and diagnostic interval (time from first consultation to diagnosis). We investigated these intervals of sarcoma survivors and identified factors associated with prolonged intervals.

Methods

We conducted a cross-sectional study among adult sarcoma patients, 2-10 years after diagnosis. Patients completed a questionnaire on their total interval, which was linked to clinical data from the Netherlands Cancer Registry. Descriptive statistics were used to describe intervals. Based on Dutch clinical guidelines, a diagnostic interval ≥1 month was considered prolonged, an interval ≥3 months as very long. Multivariable regression analyses investigated associations between patient and tumor characteristics, and interval length.

Results

1099 participants were included (response rate 58%); 60% reported a patient interval ≥1 month and 36% ≥3 months. Risk factors for a very long patient interval were sarcoma of skin, pelvis, liposarcoma or rhabdomyosarcoma. Stage III disease was associated with a shorter patient interval. Diagnostic interval length was ≥1 month in 55%, ≥3 months in 28%; risk factors for a very long diagnostic interval were being female, aged <70, or having a synovial sarcoma or chordoma.

Conclusion

Patient and diagnostic interval length were prolonged in a substantial proportion of this sarcoma survivorship population. Factors associated with length of patient or diagnostic interval differed. Creating awareness among (especially young) patients to consult a doctor and awareness among doctors to consider a sarcoma diagnosis will contribute to optimization of the total interval.

Keywords: sarcoma, survivorship, diagnostic interval, patient interval, diagnostic pathway, cancer diagnosis, delay to diagnosis

Introduction

Sarcomas are a group of solid malignant mesenchymal tumors, with more than 70 histological subtypes[1]. They have considerable heterogeneity with respect to age of onset, anatomic location, speed of progression, and outcome. Approximately 80% of sarcomas originate in soft tissue(STS) and 20% in bone(BS). Sarcomas form a typical example of rare cancer, with an estimated incidence of 4-5 per 100 000 per year[2]. Patients with rare cancers have a higher mortality rate than those with common cancers. Delayed diagnostic pathways, lack of expert pathologists, absence of rare tumour-specific multidisciplinary meetings, cancer-specific therapies and clinical trials often preclude rare cancer patients from receiving proper, timely diagnosis and care[3].

Sarcoma patients may experience long intervals to diagnosis, and the time to diagnosis has been measured frequently[4]. Total intervals for BS were 9-120.4 weeks, and 4.3-614.9 weeks for STS. However, these studies often describe small cohorts and are heterogeneous regarding inclusion criteria and study designs. Several theoretical models exist to describe time to cancer diagnosis. For research purposes it is important to work with a standardised framework with clear definitions of each event and time interval within the diagnostic pathay. In this paper we use the influential model developed by Olesen et al[5]. The time to diagnosis, the time between first symptoms and (histological) diagnosis, is known as the total interval, which can be divided into a patient and diagnostic interval[5, 6].

The current interest in a prolonged interval in general is mainly based on the assumption that early diagnosis will lead to better survival. As research on diagnostic intervals mainly focusses on patients newly diagnosed with sarcoma, no data are available on survivors and their recall from the total interval. In other cancer diagnosis, prolonged total intervals lead to worse outcomes[7]. This knowledge led to optimization the diagnostic pathway for several types, e.g. by introducing fast referral pathways or performing multiple additional investigations on one day. It is therefore important to identify risk groups for a prolonged interval, in order to study whether these strategies would improve outcomes for sarcoma patients as well. We aim to describe the total interval and its components of sarcoma survivors, and to identify patient and tumor characteristics to define risk groups for prolonged intervals.

Methods

Study design and participants

This population-based cross-sectional study included sarcoma survivors aged ≥18, registered in the Netherlands Cancer Registry (NCR), and diagnosed with sarcoma

between 1-1-2008 and 31-12-2016 at one of the six participating sarcoma expertise centers (Radboudumc Nijmegen, The Netherlands Cancer Institute Amsterdam, University Medical Center Groningen, Leiden University Medical Centre, Erasmus MC Cancer Institute Rotterdam, Maastricht University Medical Centre), regardless of their current disease status(Appendix 1 includes the selected morphology codes derived from ICD-O[8]). Exclusion criteria were cognitive impairment, too ill (judged by their (ex-) treating physician) or deceased at time of the study, unverifiable address, or inability to read and write in Dutch. Patients with desmoid fibromatosis, grade 1 chondrosarcoma, atypical lipomatous tumors or giant-cell tumors were excluded due to the indolent clinical behavior and less aggressive treatment strategies for these histological subtypes. In addition, patients with gastrointestinal stromal tumors were excluded. The NCR compiles data of all individuals newly diagnosed with cancer in the Netherlands[9]. Data registration is done by employees of the Netherlands Comprehensive Cancer Organization (IKNL) and includes patient and tumor characteristics. The main pathology source is the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA)[10].

Ethical approval was given by the medical ethical committee of Radboud University Medical Centre (2017-3944). According to Dutch law, approval of one ethical committee for questionnaire research is valid for all participating centres. The study was registered in the Dutch Trial Registry (NTR-7253).

Recruitment and data collection

Eligible patients received a letter from their (ex-)treating physician explaining the purpose of the study. Patients provided informed consent to participate and agreed to linkage of questionnaire data with their clinical data in the NCR. Data collection was conducted from October 2018 till June 2019 within PROFILES (Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship; www.profilesregistry.nl). PROFILES is a data management system for the study of the physical and psychosocial impact of cancer and its treatment. Questionnaires could be completed online or upon request by pencil-and-paper. Paper questionnaires were returned and then scanned to digitalize the data. Further details of the data collection method have been described previously[11]. Responders were compared to non-responders: patient and clinical characteristics registered in the NCR were anonymously compared on group-level

Study measures

While the study was primarily designed to examine HRQoL among sarcoma survivors, compared to an age- and sex-matched normative population (https://www.trialregister.nl/trial/7048; NTR-7253), the current study is a secondary analysis and aims to describe the total interval and its components of sarcoma survivors, and to identify patient and tumor characteristics to define risk groups for prolonged intervals. Questions on patient and

diagnostic interval were designed by the study group to match time intervals and events as defined in our adapted version of the standardized definitions proposed by Olesenet al[5, 6], as published before[4]. The diagnostic interval can be further divided into a primary care, secondary care, and tertiary care interval. All interval lengths were categorical and patient-reported (<2 weeks, 2 weeks-1month, 1-3 months, 3-6 months, 6-12 months, >12 months). A panel of patients gave feedback on relevance, comprehensibility, length of the questionnaire, and design of the questions.

Socio-demographic and clinical characteristics

Patient and tumor characteristics hypothesized to be of influence on total interval length were selected. Clinical data were derived from the NCR, which routinely collects data on patient and tumor characteristics including gender, age, socio-economic status (SES), date of diagnosis, histological subtype, tumor grade, localization and stage at diagnosis. Not all sarcomas are graded at diagnosis, where possible we added a grade according to the guideline at the time of the study[1]. Participants with missing grades were not excluded from further analyses. To report on clinically relevant subgroups, participants were divided into age categories at time of diagnosis (18-39; 40-70; ≥70 years). Time since diagnosis was calculated by subtracting date of questionnaire completion from the date of diagnosis. Participants were divided into categories (<2; 2-5; ≥5 years since diagnosis). SES was derived from zip codes, and is based on education, income and employment status[12]. Marital status, educational level, employment status, and number of comorbidities were measured at the time of questionnaire completion and are therefore not included in the analysis.

Statistical analyses

Characteristics of responders were compared to those of non-responders using χ^2 statistics for categorical variables and t-tests for continuous variables. Descriptive statistics were used to describe the study population, their total interval and its components. Categorical variables are presented as numbers or percentages, for continuous variables means and standard deviations are reported.

The study population was grouped by patient and diagnostic interval length. Intervals were dichotomized into <1 month versus ≥1 month, based upon previous literature and considering that campaigns about awareness of cancer symptoms usually use a cut-off of three weeks or longer for duration of new symptoms[13-15]. For the diagnostic interval the Dutch SONCOS guideline (Stichting ONCologische Samenwerking; foundation for multidisciplinary oncological collaboration) states that a period of four weeks between referral by the GP and diagnosis is acceptable[16]. In order to identify risk factors for patients with a very long patient or diagnostic interval, the same analysis were alsof performed

with a cut-off point of 3 months, based on previous cancer interval literature[14, 15, 17]. Missing items were assumed to be missing at random. Only available data were analyzed.

We performed multivariable logistic regression analyses, using a forced entry method. We built four models for four dependant variables: patient interval ≥1 month and ≥3 months, and diagnostic interval ≥1 month and ≥3 months. Based on a literature review, gender, age at diagnosis, SES, histology, stage, grade, and localization were selected as independent variables[4]. In case of multicollinearity we tried both factors in different models. The factor which resulted in the best model was chosen for further analysis. The calibration of final models was tested using Hosmer-Lemeshow goodness-of-fit test. Odds ratios(OR) and 95% confidence intervals(95%CI) are reported. All statistical analyses were performed using IBM SPSS 25.0; two-sided p-values <0.05 were considered statistically significant.

Results

A total number of 1887 (ex-)sarcoma patients were approached to participate in our study. 1099 (58%) of these provided informed consent and completed the questionnaire. Figure 1 presents the flow chart.

Responders versus non-responders

Comparative analysis of responders and non-responders found no differences in gender, time since diagnosis, and sarcoma subtype (BS versus STS)(Table 1). Non-responders were diagnosed at a younger age (50.2 versus 55.1 years, p<0.01), and had a lower SES (all p<0.05). Furthermore, their sarcomas were less often localized retroperitoneally, but more often in the skin or gynecological organs, and dermatofibrosarcoma protuberans occurred more frequently(all p<0.01).

Characteristics of participants

More than half of participants were male (54%) with a mean age at diagnosis of 55(Table 1). Mean time since diagnosis was 67 months, 76% had a soft tissue sarcoma, 47% were localized in the extremities. Only 2% had stage IV (distant metastases) disease at diagnosis.

Length of the components of total interval

Figure 2 shows the proportion of participants and their patient and diagnostic interval. The patient interval (n=982) lasted ≥1 month in 60%. Many patients waited longer than 3 months (36%), or even 12 months (15%) before consulting a doctor, 10% of patients could not remember their patient interval length. The diagnostic interval (n=1035) lasted ≥1 month in 55%, and for 28% it took ≥3 months with 9% of patients ≥12 months; 5% of patients couldn't remember.

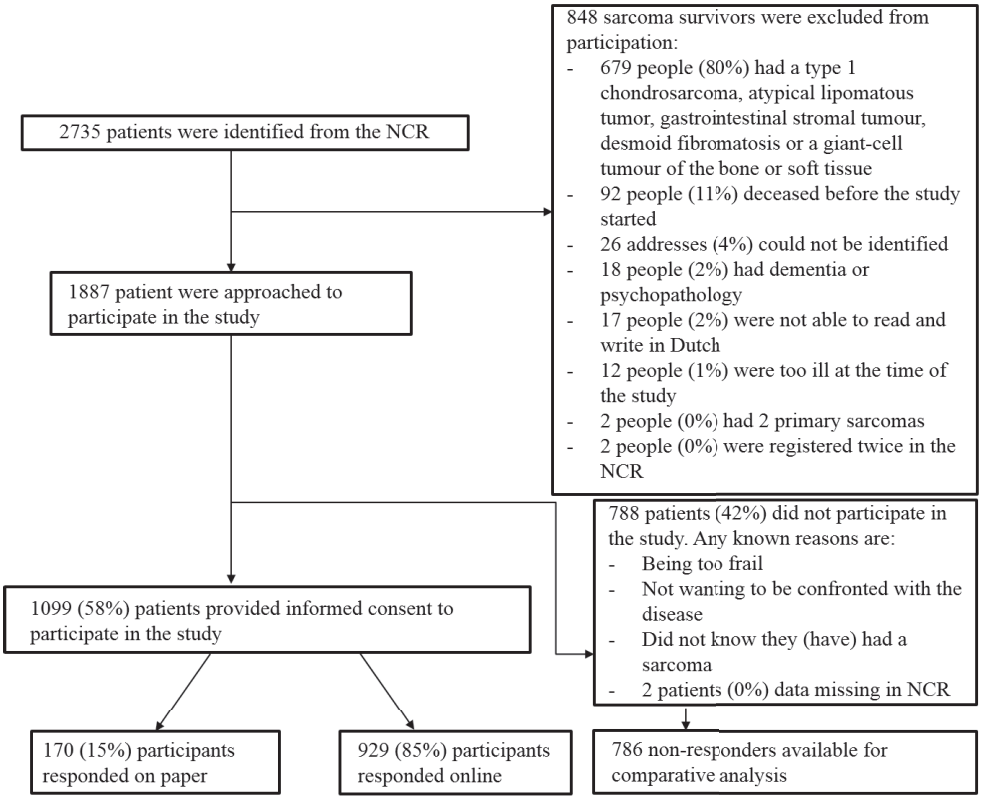

Figure 1: Flow chart

The diagnostic interval can be separated in a primary (n=899), secondary (n=964), and tertiary (n=984) care interval. Half of the patients got referred within 1 week (28%) or 1-2 weeks (23%) by their GP. Those who were not referred promptly had a very long primary care interval, of 2 weeks to 1 month (18%), 1-3 months (15%), 3-6 months (6%), 6-12 months (4%), or ≥12 months (7%). Twelve percent reported consultation of a different doctor first, whereas 4% couldn't remember their primary care interval length. The secondary care interval was <1 month in 64%, 1-3 months in 23%. Only a small proportion of patients had a longer interval of 3-6 months (7%), 6-12 months (3%), or ≥12 months (3%). Within the tertiary care interval, we saw a similar trend: 85% got diagnosed <1 month, 35% even within one week, and 30% in 1-2 weeks. Those who took longer, usually took 1-3 months (12%) with only a few participants who reported 3-6 months (2%), 6-12 months (1%), or ≥12 months (1%)(Figure 2). Patients couldn't remember the length of their secondary and tertiary care interval in 8 and 9%, respectively.

Table 1: Characteristics of responders and non-responders

	Responders	Non-responders	p-value*
Gender, no(%)			
Female	504 (46)	381 (49)	0.24
Male	595 (54)	405 (51)	
Age at time of diagnosis (years)			
mean (SD)	55.1 (15.3)	50.2 (18.7)	<0.01
Time since diagnosis (in months)			
mean (SD)	67.4 (30.3)	69.6 (30.9)	0.12
Socio-economic status, no(%)			
• Low	286 (26.1)	279 (35.6)	<0.01
• Intermediate	462 (42.1)	289 (36.8)	0.02
• High	349 (31.8)	217 (27.6)	0.05
Current marital status, no(%)		NA	NA
Married, civil partnership, or cohabiting	857 (78)		
Single, widowed, or divorced	242 (22)		
Current highest education, no(%)		NA	NA
No education, primary or secondary school	242 (22)		
Vocational qualification			
College or university	451 (41)		
	406 (37)		
Current employment status, no(%)		NA	NA
Working fill-time or part-time	451 (41)		
(Partially) disabled	99 (9)		
Other	506 (46)		
Unknown	43 (4)		
Current comorbidities, no(%)		NA	NA
0	374 (34)		
1	351 (32)		
≥2	374 (34)		
Histologic subtype, no(%)			
Bone sarcoma	264 (24)	172 (22)	0.29
Osteosarcoma	70 (6)	53 (7)	0.75
Chondrosarcoma	130 (12)	72 (9)	0.06
Chordoma	30 (3)	19 (2)	0.76
Ewing sarcoma	28 (3)	21 (3)	0.87
Other bone sarcomas	6 (1)	7 (1)	0.38
Soft tissue sarcoma	835 (76)	614 (76)	0.28
Liposarcoma	177 (16)	108 (14)	0.15
Pleomorphic liposarcoma	10 (1)	9 (1)	0.62
Myxoid liposarcoma	68 (6)	42 (5)	0.43
Undifferentiated liposarcoma	64 (6)	33 (4)	0.11
Other liposarcoma	35 (3)	24 (3)	0.86
Myxofibrosarcoma	136 (12)	89 (11)	0.48
Dermatofibrosarcoma protuberans	74 (7)	109 (14)	<0.01
Leiomyosarcoma	114 (10)	82 (10)	0.97
Rhabdomyosarcoma	15 (1)	11 (1)	0.95
Malignant peripheral nerve sheath tumor	34 (3)	24 (3)	0.96
Synovial sarcoma	35 (3)	25 (3)	0.99
Vascular sarcoma	43 (4)	27 (3)	0.59
Other soft tissue sarcoma	207 (19)	139 (17)	0.55

Table 1: Continued

	Responders	Non-responders	p-value*
Localization, no(%)			
Head and Neck	70 (6)	49 (6)	0.96
Thoracic	81 (7)	42 (5)	0.08
Abdominal excl urogenital organs	102 (9)	46 (6)	<0.01
Intraperitoneal	39 (2)	19 (2)	0.16
Retroperitoneal	63 (6)	27 (3)	0.02
Gynecological	19 (2)	29 (3)	<0.01
Urological	11 (1)	11 (1)	0.43
Extremities	514 (47)	357 (45)	0.55
Upper extremities	114 (10)	77 (10)	0.67
Lower extremities	400 (36)	280 (36)	0.72
Breast	24 (2)	18 (2)	0.88
Pelvis	84 (8)	50 (6)	0.31
Skin	121 (11)	146 (19)	<0.01
Other localization	73 (7)	38 (5)	0.10
Stage of disease, no(%)			
Stage IA	204 (19)	141 (18)	0.75
Stage IB	208 (19)	157 (20)	0.59
Stage IIA	221 (20)	119 (15)	<0.01
Stage IIB	94 (9)	57 (7)	0.30
Stage III	134 (12)	68 (9)	0.01
Stage IV	24 (2)	14 (2)	0.53
Stage IVA	4 (0)	5 (1)	0.40
Stage IVB	4 (0)	5 (1)	0.40
Unknown	206 (19)	220 (28)	<0.01
Grade		NA	NA
Low grade	615 (56)		
Intermediate or high grade	407 (37)		
Unknown	77 (7)		

Because of rounding, percentages may not add up to 100%.*Differences in continuous variables have been examined with the unpaired t-test. For differences in categorical variables, χ^2 statistics have been used. NA: not available for non-responders analysis.

A diagnostic interval ≥3 months was caused by lengthening of all components. Participants with a diagnostic interval ≥3 months (28%), had a primary care interval of ≥3 months in 50%, for secondary care and tertiary care this was 38% and 9%, respectively, versus 17%, 13%, and 4% for all participants.

Association between patient interval length and patient and tumor characteristics

Multivariabele analyses showed an association between age and patient interval ≥1 month: patients aged ≥70 at diagnosis were less likely to have a patient interval ≥1month (Table 2). This relationship lost its significance at a cut-off of 3 months. Histology, stage, and localization were associated with a patient interval ≥3 months.

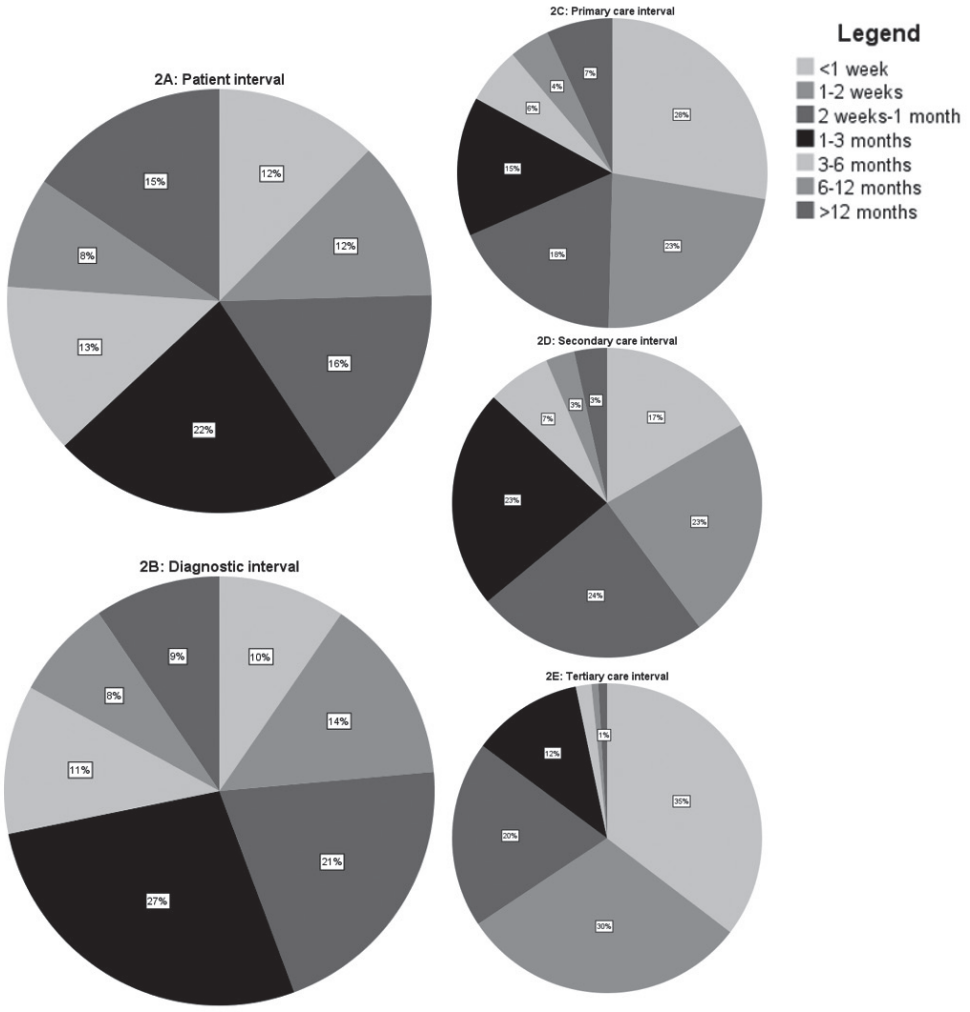

Figure 2: Percentages of participants per interval length

Association between diagnostic interval length and patient and tumor characteristics

Multivariable analysis showed an association between age at diagnosis and diagnostic interval ≥1month: patients aged ≥70 were less likely to have a long diagnostic interval(Table2). This association remained significant at a cut-off of 3 months. Gender was associated with a diagnostic interval ≥3 months as well: females were more likely to experience a long diagnostic interval.

Table 2: Multiple regression analysis of association between patient and diagnostic interval and clinical and sociodemographic factors

	Patient interval ≥1 month n=872		Patient interval ≥3 months n=872		Diagnostic interval ≥1 month n=915		Diagnostic interval ≥3 months n=915	
	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Gender								
• Male								
• Female	1.2	0.9-1.6	1.0	0.7-1.3	1.3	1.0-1.7	1.4*	1.1-2.0
Age at diagnosis (years)								
• 18-39								
• 40-69	0.8	0.5-1.2	1.1	0.7-1.6	0.8	0.5-1.1	0.7	0.5-1.0
• ≥70	0.5*	0.3-0.9	0.7	0.4-1.2	0.5*	0.3-0.8	0.5*	0.3-0.9
Socio-economic status								
• Low								
• Intermediate	0.9	0.6-1.3	0.9	0.6-1.3	0.9	0.6-1.3	1.0	0.7-1.5
• High	1.0	0.7-1.4	0.8	0.5-1.1	1.0	0.7-1.4	1.3	0.9-2.0
Histology								
Dermatofibrosarcoma protuberans								
Liposarcoma	0.3	0.1-1.0	0.3*	0.1-1.0	1.3	0.4-3.5	0.7	0.2-2.3
Myxofibrosarcoma	0.4	0.1-1.3	0.3*	0.1-1.0	1.4	0.5-4.0	0.8	0.2-2.8
Leiomyosarcoma	0.5	0.2-1.6	0.4	0.1-1.1	1.5	0.6-4.1	0.8	0.2-2.6
Rhabdomyosarcoma	0.2	0.0-1.1	0.1*	0.02-0.8	0.7	0.2-3.1	0.8	0.1-4.6
MPNST	0.5	0.1-2.4	0.5	0.1-2.5	1.1	0.2-5.1	1.0	0.2-5.2
Synovial sarcoma	1.4	0.3-6.1	0.5	0.1-1.9	3.4	0.9-13.4	2.5	0.6-10.5
Vascular sarcoma	**	**	**	**	**	**	**	**
Other soft tissue sarcoma	0.4	0.1-1.2	0.3*	0.1-0.8	1.5	0.6-4.0	0.9	0.3-2.8
Osteosarcoma	0.5	0.1-1.8	0.3	0.1-1.1	1.3	0.4-4.0	0.8	0.2-3.0
Chondrosarcoma	0.8	0.2-2.6	0.6	0.2-2.0	2.0	0.7-5.7	1.3	0.4-4.6
Chordoma	0.5	0.1-2.3	0.6	0.1-2.3	1.8	0.5-7.2	2.9	0.6-13.7
Ewing sarcoma	0.5	0.1-2.2	0.7	0.2-2.8	0.5	0.1-1.8	0.9	0.2-4.3
Other bone sarcoma	0.5	0.1-3.2	0.3	0.1-1.7	0.7	0.1-3.7	1.0	0.2-6.3
Clinical staging								
• Stage I								
• Stage II	1.0	0.7-1.4	1.0	0.7-1.5	0.8	0.5-1.2	1.0	0.6-1.5
• Stage III	0.8	0.5-1.4	0.5*	0.3-0.9	0.6	0.4-1.0	0.9	0.5-1.7
• Stage IV	0.8	0.4-1.7	1.0	0.4-2.1	0.6	0.3-1.3	0.4	0.2-1.0
Grade								
• Low grade								
• Intermediate or high grade	1.1	0.7-1.6	1.3	0.8-2.0	1.2	0.8-1.7	0.8	0.5-1.3
Localisation								
• Head and neck								
• Thoracic	1.5	0.7-3.3	1.7	0.7-3.9	1.4	0.7-3.2	0.8	0.3-1.8
• Abdominal	1.0	0.5-2.2	1.4	0.6-3.4	0.6	0.3-1.2	0.9	0.4-2.2
• Breast	***	***	***	***	***	***	***	***
• Skin	2.2	0.8-6.5	3.3*	1.1-10.1	0.8	0.3-2.2	0.7	0.2-2.5
• Pelvis	2.1	1.0-4.5	2.6*	1.2-6.0	0.6	0.3-1.3	0.8	0.3-1.8
• Upper extremities	1.4	0.7-2.9	1.8	0.8-3.9	1.0	0.5-2.1	1.1	0.5-2.4
• Lower extremities	1.7	0.9-3.2	1.8	0.9-3.7	0.8	0.4-1.4	1.0	0.5-1.9
• Other	1.5	0.5-4.1	1.4	0.5-4.3	1.7	0.6-4.9	1.5	0.5-4.4

The first category is the reference category; *p<0.05; MPNST: malignant peripheral nerve sheath tumor. **n=2 for multivariable analysis, therefore unreliable OR (>10.000) and 95% (0.0-infinite). ***n=7 for multivariable analysis, therefore unreliable OR. Chi-square of model for patient interval ≥1 month: 73.111 (p=0.000); ≥3 months 84.146 (p=0.000); diagnostic interval ≥1 month 55.122 (p=0.003); ≥3 months 57.271 (p=0.002).

Discussion

In this cross-sectional survivorship study, we described the total interval of adult sarcoma patients as reported by the sarcoma survivors and identified factors associated with patient and diagnostic interval length. To our knowledge our study is the largest to report on the route to diagnosis of adult sarcoma patients.

We found the length of the total interval of adult sarcoma patients to be highly variable due to different patient and diagnostic intervals, which is in line with existing literature.

The patient interval was long (≥1 month) in 60%, and very long (≥3 months) in 36%. The hypothesis that low stage, indolent sarcomas do not trigger patients to seek help, is supported by our findings and due to our survivorship patient selection. Tumors located in the pelvis often cause npn-specific symptoms causing patients to delay a visit to their GP. Stage III tumors often grow rapidly, causing patients to seek help as soon as they experience symptoms. Similar results were found in a British adult sarcoma study[17]. A review amongst other cancer patients, with mostly retrospective data, found contradictory results: older age was associated with patient delay for breast cancer, whereas there was inconclusive evidence or no impact on patient interval length in upper gastro-intestinal, gynecological, colorectal, urological, and lung cancer[18]. Similar to findings in our study, gender and SES were not associated with patient interval length in most cancers, although patients with a lower SES who had upper gastro-intestinal or urological cancer waited longer.

The diagnostic interval was long (≥1 month) in 55%, and very long (≥3 months) in 28%. A long diagnostic interval was not based on one specific component, but remarkably on all its components (primary, secondary, and tertiary care interval). These are important findings because improving the patient, diagnostic and referral pathway could thus be highly profitable in reducing the total interval length. It is difficult to compare our findings with other sarcoma studies, as in general those studies included mainly children. However, the trend of younger patients having longer diagnostic intervals was also seen in a British adult sarcoma study[17] and is generally seen amongst other cancer subtypes such as breast, upper gastro-intestinal, and pancreatic carcinoma, although results are contradictory for several other cancer types in different studies[18, 19]. Furthermore, the latter study by Din et al only included patients aged ≥40 and these results are thus not directly comparable.

In our study, the secondary care interval lasted less than 4 weeks in 57%, however, it lasted more than a month for 33% of patients. According to Dutch guidelines, the secondary

interval should not last more than 4 weeks[16] unless a patient is being referred to a different healthcare facility, such as a sarcoma centre, when an additional three weeks may be added to the interval. An important number of patients does thus not receive a diagnosis within this time limit. The tertiary care interval was <1 month for 78% of patients. This proportion may be overestimated due to a group of patients diagnosed with sarcoma at the referring hospital, and who thus received their diagnosis before or at the first appointment (e.g. within a week: 32%).

The question arises whether the proportion of prolonged intervals found in our study is due to healthcare system factors. The Dutch curative healthcare sector is financed by taxes and obligatory personal healthcare insurances, with which care by a GP does not result in additional costs for the patient. Almost all citizens are registered with a particular GP, which they need to consult to be referred for hospital care. In the Netherlands, there is no private sector for sarcoma care. Literature on whether healthcare system factors influence total interval length is scarce and studies with direct comparisons are lacking. Future research should ideally have an international design, which enables the evaluation of the contribution of healthcare system factors on total interval length.

Our study had a response rate of 58%, which is high considering decreasing response rates in cross-sectional surveys[20-23]. Although non-responders were slightly younger and had a lower SES than responders, they showed an equal distribution of gender, time since diagnosis, and rate of BS versus STS and we therefore assume that our study is representative for all sarcoma patients with a 2-10-year survival after diagnosis. However, due to the survivorship nature of the study, there is a selection bias in which elderly with significant co-morbidities, primary metastatic patients and patients with low literacy are probably underrepresented in this cohort[24]. Another part of this selection bias is that we invited patients diagnosed or treated at six sarcoma centers and may have missed patients treated in regional hospitals, who probably had more superficial and low-grade sarcomas.

A second limitation is that our data were patient-reported and subject to recall bias. However, when given the choice to indicate whether they could or could not remember the time intervals, 90% and 95% of patients indicated they still remembered their patient and diagnostic interval length, respectively. Furthermore, time since diagnosis was not associated with either length of patient or diagnostic interval(data not shown). A generally consistent research finding is that as the recall time increases, the ability to recall events, begins to degrade[25]. However, significant events, such as a cancer diagnosis, are less likely to be forgotten[25]. Furthermore, estimation of duration of an event is extremely stable[26]. To minimize the effect of recall bias in our study, patients had to report duration of intervals instead of exact dates, questions were anchored to a life event (cancer

diagnosis), history had to be recalled in a chronological fashion, and comprehensibility of questions was checked by patient.

Further research is needed to understand the exact reasons and consequences of long diagnostic intervals. Our study group currently conducts a prospective, longitudinal, international study called QUEST: "QUality of life and Experiences of Sarcoma Trajectories", to investigate the total interval in more detail and to link its length to both clinical and patient-reported outcomes(clinical trials record 2017-3881). The international design of this study allows for comparison of healthcare system factors, as well as patient and tumor characteristics. Its prospective design enables us to include all patients, including those with incurable disease and aggressive subtypes. Furthermore, understanding of the consequences of long diagnostic intervals will enable the sarcoma community to develop strategies to reduce diagnostic delay, including creating awareness among the general population and doctors (such as the 'golf ball campaign') and expert and fast comprehensive diagnostics at sarcoma centers.

Conclusion

The time to diagnosis of adult sarcoma patients who have survived 2-10 years after diagnosis is highly variable, and both patient and diagnostic interval contribute to a long total interval. More than half of our participants had a patient and diagnostic interval of ≥1 month or even ≥3 months in about a third of cases. Risk factors for a very long patient interval were sarcomas in the skin or pelvis, whereas having a liposarcoma, myxofibrosarcoma, rhabdomyosarcoma or other STS, and stage III disease lead to a shorter interval. Risk factors for a very long diagnostic interval were being female or aged 18-69. As the effect of a prolonged interval on outcomes remains unclear in terms of morbidity, HRQoL, and survival, we should prioritize in depth analysis of all contributing factors in patients and healthcare systems which are responsible for diagnostic delays. Analyzing this will result in recommendations which enable optimization of the total diagnostic trajectory for sarcoma patients.

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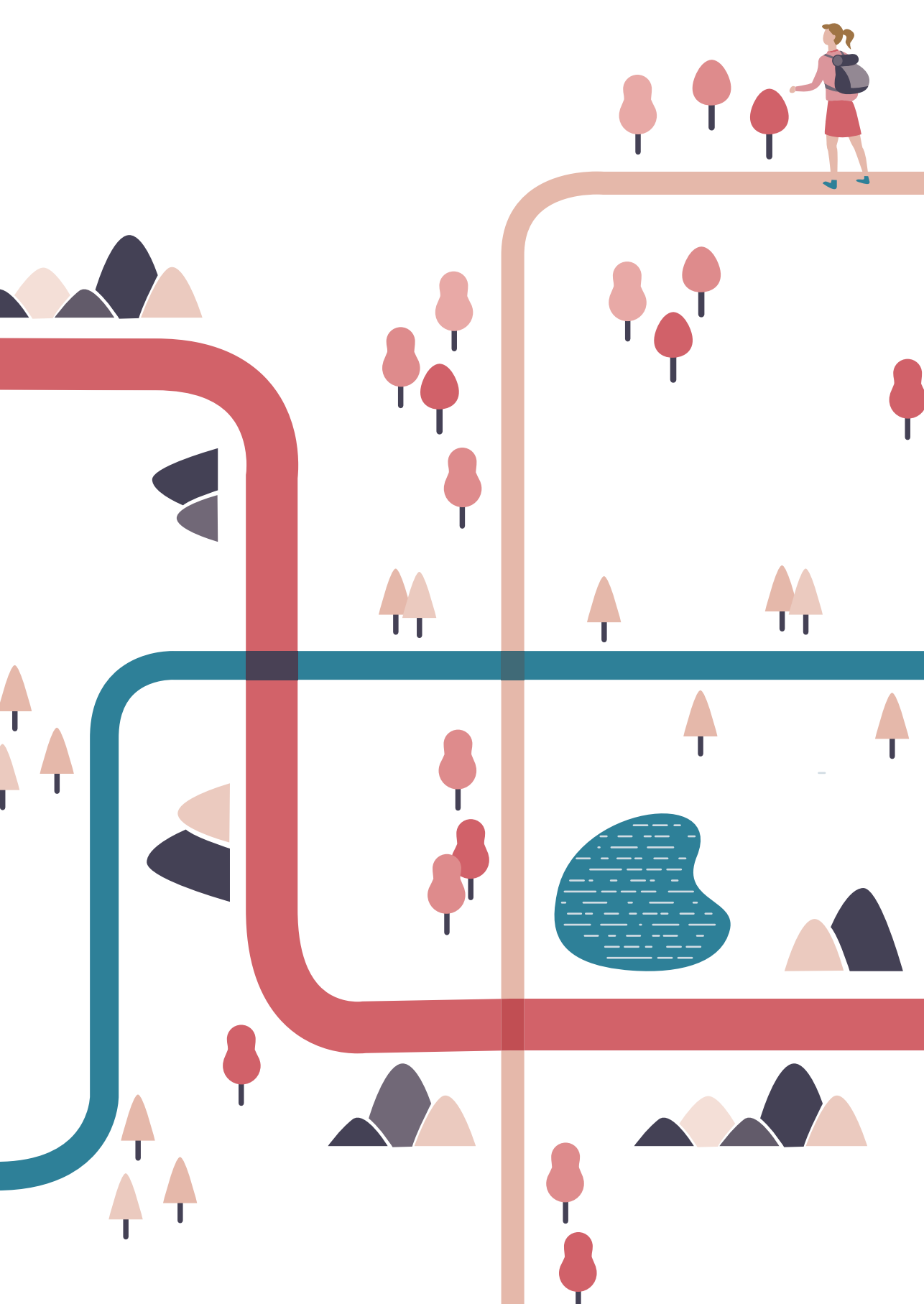

CHAPTER 5

The perceived impact of length of the diagnostic pathway is associated with health-related quality of life of sarcoma survivors: results from the Dutch nationwide SURVSARC study

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Abstract

Background

Sarcoma patients often experience a long time to diagnosis, known as the total interval. This interval can be divided into a patient (time from symptom to doctor consultation) and diagnostic interval (time from first consultation to diagnosis). In other cancers, a long total interval has been associated with worse outcomes, but its effect on health-related quality of life (HRQoL) has never been investigated among sarcoma patients. This study investigates the association between (1)actual time to diagnosis and HRQoL; (2)perceived impact of diagnostic interval length and HRQoL; (3)actual length and perceived impact of length on HRQoL of sarcoma survivors.

Methods

A cross-sectional study was performed among sarcoma patients aged ≥18, diagnosed 2-10 years ago in the Netherlands. Participants completed a questionnaire on HRQoL, time to diagnosis, perceived impact of diagnostic interval on HRQoL, and coping.

Results

1099 participants were included (response rate 58%). The mean time since diagnosis was 67.4 months. More than half reported a patient (60%) or diagnostic interval (55%) ≥1 month. A third (31%) perceived a negative impact of their diagnostic interval length on HRQoL. Patient or diagnostic interval length were not associated with HRQoL. In contrast, participants perceiving a negative impact (32%) had lower HRQoL scores than those perceiving a positive (11%) or no impact (58%)(p=0.000). This association remained significant in a multivariable model, in which maladaptive coping strategies and tumour characteristics were also found to be associated with HRQoL. Participants perceiving a negative impact of length of diagnostic interval related this to high psychological distress levels, more physical disabilities, and worse prognosis.

Conclusion

The perceived impact of diagnostic interval length was associated with HRQoL of sarcoma survivors, whereas actual length was not associated with HRQoL. Maladaptive coping strategies were independently associated with HRQoL. This offers opportunities for early intervention to improve HRQoL.

Introduction

Sarcomas are mesenchymal tumours, with considerable heterogeneity regarding age of onset, anatomic location, histological subtype, and outcome. These solid tumours consist of more than 100 histologic subtypes which originate in soft tissue (STS; 80%) or bone (BS; 20%). Sarcomas are typical examples of rare cancers (less than 6 individuals in 100,000/year), and have an estimated incidence of 4-5 per 100.000 per year[1]. Patients with rare cancer have worse outcomes than patients with common cancers: in The Netherlands the 5-year survival rate of all subtypes of STS and BS taken together is 58% and 49%, respectively, which is lower than 5-year survival rates for all cancers diagnosed in The Netherlands (65%)[2]. Given the rarity and heterogeneity of the disease, sarcomas are often not recognized by healthcare providers, leading to delayed diagnostic pathways. Also, the diagnostic process can be complex, leading to a prolonged diagnostic time in expert centres. Furthermore, a lack of expert pathologists, absence of tumour-specific multidisciplinary teams, cancer-specific therapies and clinical trials often preclude patients with rare cancer from receiving a proper, timely diagnosis and adequate care[3].

Historically, evaluation of oncologic care has focused on clinical outcomes, such as treatment-related toxicities and overall survival. Currently, more attention is being given to patient-reported outcomes, such as health-related quality of life (HRQoL). HRQoL refers to the impact of disease and treatment on domains of physical, psychological, and social functioning[4]. In other malignancies, prolonged time to cancer diagnosis has been associated with worse HRQoL[5]. The association between time to diagnosis and HRQoL has never been investigated quantitatively among sarcoma patients, but qualitative reports indicate that time to diagnosis influences patients' physical and psychosocial well-being[6, 7]. This may not only influence HRQoL on the short-term but may also influence HRQoL among sarcoma survivors.

Although survival rates of sarcoma patients lag those of common cancer patients, there are an estimated 280.000 sarcoma survivors in Europe[1] who require supportive and rehabilitation services. To improve these services, we need to understand care experiences and needs of sarcoma survivors. Survivorship care focusses on the health and well-being of a person with cancer from the time of diagnosis until the end of life[8], including issues related to follow-up care (e.g. regular health and wellness check-ups), late effects of treatment, cancer recurrence, second cancers, and HRQoL.

This study investigates the association between actual time to diagnosis and HRQoL in a group of adult sarcoma survivors. Furthermore, the perceived impact of diagnostic interval length on HRQoL, both quantitative as well as qualitative, and the independent association of time to diagnosis and other variables on HRQoL are investigated.

Methods

Study design and participants

This cross-sectional cohort study included Dutch sarcoma patients aged ≥18, registered in the Netherlands Cancer Registry (NCR), and diagnosed between 1-1-2008 and 31-12-2016 at one of the participating sarcoma expertise centres (Radboud University Medical Centre Nijmegen, Antoni van Leeuwenhoek Amsterdam-The Netherlands Cancer Institute, University Medical Centre Groningen, Leiden University Medical Centre, Erasmus MC Cancer Institute Rotterdam, Maastricht University Medical Centre). Participants had to be able to complete Dutch questionnaires by themselves. Patients with desmoid fibromatosis, grade 1 chondrosarcoma, atypical lipomatous tumour, giant-cell tumours, or gastro-intestinal stromal tumour were excluded due to their indolent clinical behaviour or different treatment strategies compared to other sarcomas. Ethical approval was given by the medical ethical committee of Radboud University Medical Centre (2017-3944) and the study was registered in the Dutch Trial Registry (NTR-7253).

Recruitment and data collection

Eligible patients received a letter from their (ex-)treating physician explaining the purpose of the study. After providing informed consent, patients could complete questionnaires either online or by pencil-and-paper. Further details of this method have been described previously [9, 10].

Study measures

While this study was primarily designed to examine HRQoL among sarcoma survivors compared to an age- and sex-matched normative population (https://www.trialregister.nl/trial/7048; NTR-7253), the current study is a preplanned, secondary analysis investigating the association between time to diagnosis and HRQoL.

Time to diagnosis

Time to diagnosis is often referred to as the total interval. The total interval, describing time from first symptom until (histological) diagnosis, can be divided into a patient and diagnostic interval[6, 11, 12]. These encompass time from first symptom until first presentation to a doctor (patient interval), and time from this first presentation until pathologic diagnosis (diagnostic interval). The diagnostic interval can be further divided into a primary care, secondary care, and tertiary care interval.

Questions on patient and diagnostic interval length were designed by the study group, all intervals were patient-reported, and answers were categorical. The study population was grouped by length of the patient and diagnostic interval, with a cut-off point of 1 month, based on previous literature[13-16]. Many countries quantify four weeks or one month for the diagnostic interval as appropriate and also the Dutch SONCOS guideline

(Stichting ONCologische Samenwerking; foundation for multidisciplinary oncological collaboration) accepts a period of four weeks between referral by the GP and histological cancer diagnosis[17].

Health-related quality of life: EORTC QLQ-C30

HRQoL was measured by the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30). This self-administered 30-item questionnaire has been validated to measure HRQoL in cancer patients[18]. It consists of a global health status, five functional scales, three symptom scales, and several single items assessing additional symptoms and perceived financial impact of the disease. The global health status is the patient's rating of his overall health and quality of life during the past week; the functional scales assess physical, cognitive, role, social, and emotional functioning. Global QoL and the functioning scales were used in our analyses. After linear transformation of the raw scores, all scores range from 0 to 100; a higher score represents a better global health status or level of functioning[19]. Apart from a quantitative score, one can examine clinical relevance using the guidelines of Cocks et al; they distinguish four effect sizes: trivial, small, medium, or large[20]. Each scale has its own threshold between size classes. A guideline for the interpretation of the clinical impact of emotional functioning is missing, therefore the cut-off points of role functioning were used, as this is the most conservative scale and this method has been described previously[21].

Perceived impact of diagnostic interval length on HRQoL

This was assessed by a single question: 'Do you think your HRQoL was influenced by your diagnostic interval length?', and the option for patients to explain their multiple-choice answer (yes, negatively; yes, positively; or no) in an open text field.

Socio-demographic and tumour characteristics

Tumour characteristics were available from the NCR, which routinely collects data of all individuals newly diagnosed with cancer. These include date of diagnosis, histology, tumour grade, localisation, and stage at diagnosis, as well as several patient characteristics such as age at diagnosis, gender and socio-economic status(SES). Patients were grouped into clinically relevant subgroups based on age (18-39; 40-69; ≥70 years old). SES was derived from zip codes, and is based on education, income and employment status[22]. Date of participation was subtracted from date of diagnosis to calculate time since diagnosis. The treatment modalities were patient-reported and include all treatments patients have had since their primary diagnosis.

Coping

Coping, the way an individual conducts oneself to decrease the effect of a stressful situation[23], was assessed using the Illness Cognition Questionnaire for chronic diseases

(ICQ)[24]. This 18-item questionnaire consists of three cognition subscales of six items rated on a 4-point Likert scale: helplessness as a way of emphasizing the aversive meaning of the disease; acceptance as a way to diminish the aversive meaning; and perceived benefits as a way of adding a positive meaning to the disease[24]. Total subscale scores could range from 6 to 24, with higher scores on helplessness, and lower scores on acceptance and disease benefits indicate maladaptive coping strategies. Adaptive coping means that one evaluates the situation, actively seeks for help, considers all thinkable solutions and actively tries to solve the problem, while maladaptive coping means one will try to move away from the stressful event, indicating that the problem will not be solved.

Statistical analyses

Descriptive statistics were used to describe the study population. Categorical variables are presented as numbers and percentages, for continuous variables, means and standard deviations are reported.

To investigate the association between patient and diagnostic interval length, perceived impact of length of diagnostic interval and HRQoL (global health status and all five functioning scales), a series of one-way analysis of variance (ANOVA) were conducted, with a cut-off point of 1 month.

The independent association between interval length, perceived impact of diagnostic interval on HRQoL, and patient and tumour characteristics and coping strategies were tested using multivariable linear regression analyses (for global health status and all five functioning scales).

Open field answers given by patients who described a negative impact of their diagnostic interval length on HRQoL were analysed by two investigators (VS and OH) using inductive coding, followed by axial coding to define main themes. Quotes to illustrate the results were selected.

Missing items in the multi-item domains of the EORTC-QLQ-C30 were imputed with simple mean imputation, according to the guidelines of the EORTC Quality of Life Group[19]. After imputation of these values an available cases analysis was performed. All other missing data were assumed to be missing at random, and only available data were analysed. All statistical analyses were performed using IBM SPSS 25.0; two-sided p-values of <0.05 were considered statistically significant.

Results

Participants

We included 1099 of 1887 invited sarcoma patients (response rate 58%). The flow-chart and characteristics of responders have been published before[9]. Responders were diagnosed at a mean age of 54.6 years, 54% were male, mean time since diagnosis was 67.4 months, 76% were diagnosed with STS and 47% of sarcomas were located in the extremities (Table 1).

Health-related quality of life by patient and diagnostic interval length

The patient interval lasted ≥1 month in 60% (n=589). The diagnostic interval lasted ≥1 month in 55% (n=569). No statistical differences in HRQoL were found for the different patient and diagnostic interval groups (Figure 1A).

Influence of perceived impact of diagnostic interval on HRQoL

More than half of participants (58%, n=620) thought their HRQoL was not influenced by their diagnostic interval length, whilst 31% (n=337) and 11% (n=115) thought their HRQoL was influenced negatively or positively by their diagnostic interval length.
In all domains, patients with a perceived negative impact of diagnostic interval length on

HRQoL scored significantly lower compared to the patients with no or a positive perceived impact. (Figure 1B). All these differences showed a small clinically relevant difference as well, both between the groups who perceived a negative impact versus the group experiencing a positive impact or no impact. There was no difference between the group experiencing a positive impact and those experiencing no impact.

Independent association of patient interval and patient and tumour characteristics on HRQoL

Global health status was independently associated with perceived impact of diagnostic interval length on HRQoL (Table 2). Participants perceiving a positive or no impact, had a higher global health status than those perceiving a negative impact. Furthermore, participants with a lower global health status score showed maladaptive coping strategies, with higher scores on helplessness and lower scores on acceptance and disease benefits. Several tumour characteristics were associated with global health status.

Table 1: participant characteristics

	All patients (n=1099)
Gender n (%)	
• Male	595 (54)
• Female	504 (46)
Age at diagnosis in years: Mean (SD)	54.6 (15.4)
Socio-economic status n (%)	
• Low	286 (26.1)
• Intermediate	462 (42.1)
• High	349 (31.8)
Coping: mean (SD)	
• Helplessness	8.8 (3.6)
• Acceptance	18.8 (4.2)
• Disease benefits	15.8 (4.8)
Time since diagnosis in months: Mean (SD)	67.4 (30.4)
Location n (%)	
• Extremities	514 (47)
• Non-extremities	585 (53)
Histology n (%)	
Soft tissue sarcoma	835 (76)
• Dermatofibrosarcoma protuberans	74 (7)
• Liposarcoma	177 (16)
• Myxofibrosarcoma	137 (13)
• Leiomyosarcoma	113 (10)
• Rhabdomyosarcoma	15 (1)
• MPNST	34 (3)
• Synovial sarcoma	35 (3)
• Vascular sarcoma	43 (4)
• Other soft tissue sarcoma	201 (18)
Bone sarcoma	264 (24)
• Osteosarcoma	69 (6)
• Chondrosarcoma	130 (12)
• Chordoma	30 (3)
• Ewing sarcoma	28 (3)
• Other bone sarcoma	13 (1)
Grade n (%)	
• Low grade	614 (60)
• Intermediate or high grade	407 (40)
Metastases at diagnosis n (%)	
• Not present	1067 (97)
• Present	32 (3)
Treatment modalities n (%)	
• Surgery	448 (43)
• Surgery and radiotherapy	422 (41)
• Surgery and chemotherapy	79 (8)
• Surgery and radiotherapy and chemotherapy	86 (8)

The n of an individual cell may be smaller due to missing values. Participants who had only undergone radiotherapy, chemotherapy or a combination of the two were excluded from this analysis, due to their small group size and unreliable analysis.

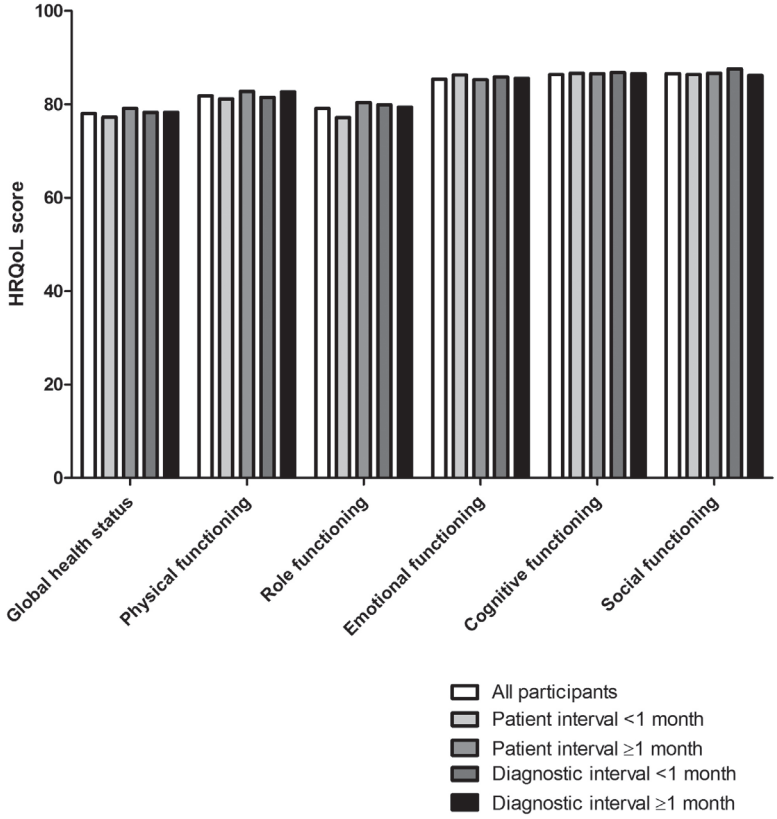

Figure 1A: Mean scores on HRQoL

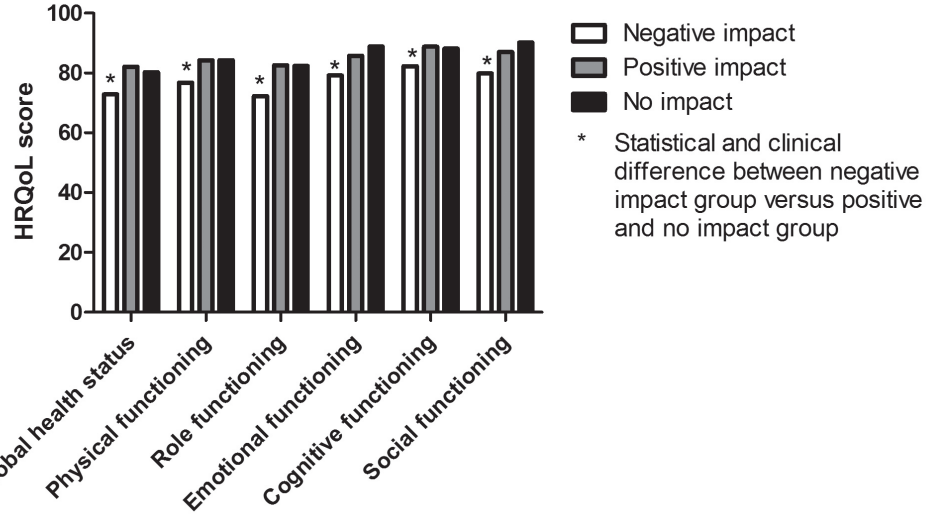

Figure 1B: Mean HRQoL scores by impact of diagnostic interval on HRQoL

Table 2: Standardized betas of multivariable linear regression analysis evaluating the association of patient interval and other variables with EORTC QLQ-C30 scales

	Global health status	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Patient interval						
<1 month	ref	ref	ref	ref	ref	ref
≥1 month	0.031	0.017	0.047	-0.032	-0.006	-0.008
Perceived impact of diagnostic interval length						
-negative	ref	ref	ref	ref	ref	ref
-positive	0.088**	0.040	0.044	0.026	0.051	0.027
-no impact	0.065*	0.032	0.034	0.092**	0.044	0.086**
Gender						
-male	ref	ref	ref	ref	ref	ref
-female	-0.038	-0.064*	0.009	-0.039	-0.042	-0.010
Age at diagnosis	-0.018	-0.231**	-0.086**	0.174**	0.103**	0.071*
Socio-economic status						
-low	ref	ref	ref	ref	ref	ref
-intermediate	0.029	0.060*	0.007	0.014	-0.019	0.018
-high	0.034	0.062*	0.029	0.020	0.044	0.038
Coping						
-helplessness	-0.441**	-0.601**	-0.601**	-0.386**	-0.323**	-0.518**
-acceptance	0.157**	-0.005	0.063*	0.239**	0.113**	0.122**
-disease benefits	0.118**	0.017	0.030	0.010	0.013	0.011
Time since diagnosis	-0.036	-0.064**	-0.035	0.042	0.005	-0.006
Location						
-non-extremity	ref	ref	0.0(ref)	ref	ref	ref
-extremity	0.081**	-0.060*	0.037	0.049	0.106**	0.045
Histology#						
-dfsp	ref	ref	ref	ref	ref	ref
-liposarcoma	-0.103*	0.041	0.063	0.12	0.061	0.000
-myxofibros.	-0.135**	0.013	0.013	-0.025	-0.020	-0.035
-leiomyos.	-0.058	0.036	0.087*	-0.026	-0.018	0.040
-rhabdomyos.	0.011	0.011	0.042	0.018	0.031	0.044
-mpnst	0.000	-0.065*	-0.005	0.010	0.002	0015
-synovial sarcoma	-0.037	0.015	-0.014	0.013	0.019	0.002
-vascular sarcoma	-0.014	-0.019	-0.001	-0.020	0.023	-0.006
-other STS	-0.132*	0.041	0.049	0.078	0.028	0.034
-osteosarcoma	-0.053	-0.098**	-0.049	0.067	0.026	0.026
-chondros.	-0.075	-0.048	-0.041	0.061	0.010	0.011
-chordoma	-0.125**	-0.102**	-0.042	-0.008	0.003	-0.046
-Ewing sarcoma	-0.012	-0.033	0.010	0.080*	-0.002	0.028
-other BS	-0.042	-0.024	0.003	0.007	0.026	0.014
Grade						
-low	ref	ref		ref	ref	ref
-high	-0.059	-0.055		-0.044	-0.011	-0.014
Metastases at diagnosis						
-not present	ref	ref		ref	ref	0.0 (ref)
-present	-0.037	0.027		-0.016	-0.054	-0.038
Treatment modality^						
-surgery plus CHx, RTx or both	ref	ref		ref	ref	ref
-surgery alone	-0.009	-0.002		0.000	0.079*	0.028

#STS = soft tissue sarcoma; BS = bone sarcoma; dfsp = dermatofibrosarcoma; myxofibros. = myxofibrosarcoma; leiomyos. = leiomyosarcoma; rhabdomyos. = rhabdomyosarcoma; mpnst = malignant peripheral nerve sheath tumour; chondros. = chondrosarcoma. ^CHx = chemotherapy; RTx = radiotherapy. *= p<0.05. ** p<0.01.

Similar results were found for the functioning scales (Table 2). Coping strategies, and especially the helplessness scale, was negatively associated with all functioning scales. The perceived impact of the diagnostic interval length on HRQoL showed a similar trend for all functioning scales but was only significant for the difference between the no impact group and the negative impact group on the emotional and social functioning scale. Age was associated with all functioning scales, and gender, SES, and time since diagnosis were associated with physical functioning.

Independent association of diagnostic interval and patient and tumour characteristics on HRQoL

Although diagnostic interval length was not associated with global health status, the perceived impact of diagnostic interval length remained significantly associated (Table 3). Participants perceiving a positive or no impact have a higher global health status. Those with maladaptive coping strategies had lower global health status scores. Both location and histology were associated with global health status in the model including patient interval length.

Table 3: Standardized betas of multivariable linear regression analysis evaluating the association of diagnostic interval and other variables with EORTC QLQ-C30 scales

	Global health status	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Diagnostic interval						
<1 month	ref	ref	ref	ref	ref	ref
≥1 month	0.012	0.016	-0.015	0.019	0.012	-0.027
Perceived impact of diagnostic interval length						
-negative	ref	ref	ref	ref	ref	ref
-positive	0.087**	0.042	0.035	0.034	0.055	0.021
-no impact	0.066*	0.035	0.027	0.099**	0.048	0.079*
Gender						
-male	ref	ref	ref	ref	ref	ref
-female	-0.037	-0.064**	0.011	-0.041	-0.043	-0.009
Age at diagnosis	-0.018	-0.230**	-0.089**	0.177**	0.104**	0.069*
Socio-economic status						
-low	ref	ref	ref	ref	ref	ref
-intermediate	0.029	0.060*	0.007	0.015	-0.019	0.018
-high	0.035	0.062*	0.030	0.019	0.044	0.038
Coping						
-helplessness	-0.441**	-0.600**	-0.604**	-0.384**	-0.322**	-0.520**
-acceptance	0.157**	-0.005	0.064*	0.238**	0.113**	0.122**
-disease benefits	0.117**	0.017	0.027	0.012	0.014	0.010
Time since diagnosis	-0.036	-0.066**	-0.035	0.042	0.005	-0.007
Location						
-non-extremity	ref	ref	ref	ref	ref	ref
-extremity	0.083**	-0.059*	0.040	0.046	0.105**	0.045

Table 3: Continued

	Global health status	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Histology#						
-dfsp	ref	ref	ref	ref	ref	ref
-liposarcoma	-0.110*	0.037	0.054	0.017	0.061	0.003
-myxofibros.	-0.141**	0.009	0.005	-0.020	-0.020	-0.032
-leiomyos.	-0.062	0.033	0.083*	-0.024	-0.018	0.043
-rhabdomyos.	0.008	0.009	0.038	0.021	0.031	0.045
-mpnst	-0.003	-0.067*	-0.007	0.010	0.002	0.017
-synovial sarcoma	-0.039	0.013	-0.012	0.011	0.017	0.005
-vascular sarcoma	-0.018	-0.022	-0.006	-0.017	0.023	-0.004
-other STS	-0.139**	0.037	0.040	0.084	0.029	0.038
-osteosarcoma	-0.055	-0.100**	-0.051	0.068	0.026	0.028
-chondros.	-0.079	-0.051	-0.042	0.061	0.009	0.015
-chordoma	-0.127**	-0.103**	-0.042	-0.008	0.003	-0.044
-Ewing sarcoma	-0.013	-0.034	0.008	0.081*	-0.001	0.029
-other BS	-0.044	-0.025	-0.001	0.009	0.026	0.014
Grade						
-low	ref	ref	ref	ref	ref	ref
-high	-0.058	-0.054	-0.011	-0.044	-0.010	-0.015
Metastases at diagnosis						
-not present	ref	ref	ref	ref	ref	ref
-present	-0.037	0.027	0.005	-0.017	-0.054	-0.037
Treatment modality^						
-surgery plus CHx, RTx or both	ref	ref	ref	ref	ref	ref
-surgery alone	-0.006	-0.001	0.037	-0.003	0.078*	0.028

#STS = soft tissue sarcoma; BS = bone sarcoma; dfsp = dermatofibrosarcoma; myxofibros. = myxofibrosarcoma; leiomyos. = leiomyosarcoma; rhabdomyos. = rhabdomyosarcoma; mpnst = malignant peripheral nerve sheath tumour; chondros. = chondrosarcoma. ^CHx = chemotherapy; RTx = radiotherapy. *= $p<0.05$. ** $p<0.01$.

On the functioning scales coping strategies, especially the helplessness and acceptance scales, remained independently associated. Age at diagnosis, gender, SES, and a longer time since diagnosis remained associated as well.

Considerations of patients who perceive a negative impact of their diagnostic interval length on HRQoL; qualitative analyses

We identified three main themes: psychological distress, physical inability, and influence on prognosis. Of the patients who commented on why their HRQoL was influenced negatively by their diagnostic interval length (n=298), 52% said this was due to psychological distress: an increase of insecurity, fear, and stress. 73% of these participants had a diagnostic interval length ≥1 month, 39% ≥3 months. They experienced these emotions not only during the diagnostic trajectory, but also in their current lives. They feared recurrence of disease, metastases or death.

'Fear, you don't know when and where it recurs. You continuously monitor your body.'
'Heavy psychological stress during the diagnostic trajectory.'

Many (41%) reported more physical inability due to longer lasting complaints, growth of the tumour and consequently more elaborate treatment, such as larger operations, the addition of radiotherapy or chemotherapy. 81% of these participants reported a diagnostic interval ≥1 month, and 63% ≥3 months. Some (7%) thought it influenced their prognosis and thought metastases or disease recurrence could have been avoided with an earlier diagnosis and would have possibly led to a curative treatment. Of these, 86% experienced a diagnostic interval ≥1 month and 36% ≥3 months.

'A lot of pain longer than necessary. Surgical intervention was not possible anymore due to the long diagnostic trajectory.'
'Then they would not have to cut it out this far, so I would have fewer complaints now.'
'Yes, because if there had been an earlier intervention, then the sarcoma would not have been this large and I would not have had metastases.'
*'Due to not t*ackling it immediately it came back twice.'

Discussion

In this cross-sectional cohort study among a large sarcoma survivorship population, we found that patient and diagnostic interval length were not associated with HRQoL scores, but the perceived impact of diagnostic interval length on HRQoL was associated with HRQoL scores.

There have been no published studies looking at the effect of patient and diagnostic interval length on HRQoL among cancer survivors. However, in a systematic review about the effect of total interval length on outcomes of symptomatic cancer just after diagnosis, *Neal et al* found that earlier diagnosis of cancer will likely improve HRQoL[5].

Although patient and diagnostic interval length were not associated with HRQoL scores, we found perceived impact of diagnostic interval length on HRQoL to be independently associated with global health status and several HRQoL functioning scales. Participants perceiving a negative impact had lower HRQoL scores than those perceiving a positive or no impact. Furthermore, participants with lower HRQoL scores used maladaptive coping strategies. Participants perceiving a negative impact of their diagnostic interval on their HRQoL, showed higher scores on the subscale helplessness, and lower scores on the acceptance and disease benefits scales (data not shown). Both perceived impact and coping remained independently associated in our multivariable model. The question remains why perceived impact remains associated, this may be due to actual time to

diagnosis, or other patient or tumour characteristics. Coping strategy was also found to be a significant predictor of HRQoL among other malignancies[25-27]. The use of coping strategies can vary between patients, and over time or between situations[23]. Although probably not sarcoma specific and solely related to the diagnostic interval length, our results indicate that supportive services focussing on developing adaptive coping strategies, may positively influence patients' HRQoL.

Our finding that the perceived impact of diagnostic interval length on HRQoL is associated with HRQoL scores, is further supported by the qualitative analysis of open text field answers, in which many patients perceiving a negative impact describe psychological distress, more physical disabilities, and a worse prognosis due to their diagnostic interval length. It is worrying that 2-10 years after diagnosis, patients still report this psychological and physical burden. We are not aware of previous studies examining patients' perception of diagnostic interval length and HRQoL. However, our findings are supported by two British and two Danish studies, who which reported that cancer patients diagnosed through fast-track referrals, were less likely to be dissatisfied with length of waiting times and more likely to be satisfied with their subsequent cancer care, compared with those referred electively[28-31].

To our knowledge, this is the only study that has investigated the influence of patient and diagnostic interval length and perceived impact of diagnostic interval length on HRQoL among adult sarcoma survivors. The overall completeness of variables in our analysis sample was high.

Our study has several limitations. First, although we invited all patients diagnosed with sarcoma in The Netherlands between 2008-2016, there is a selection bias with probably an overrepresentation of patients with high health literacy. Furthermore, due to the survivorship nature of the study, there is a natural selection of patients with a favourable prognosis, less aggressive histological subtypes, and low co-morbidity. Second, our interval length data are subject to recall bias. However, 90% and 95% of patients indicated they still remembered their patient and diagnostic interval length. In general, significant events, such as cancer diagnosis, are not likely to be forgotten[32]. Furthermore, estimation of duration of an event is extremely stable[33]. Third, one may argue that a cut-ff of 1 month for diagnostic interval length for sarcomas is too short. However, a sensitivity analyses with a cut-off of 3 months, did not show different results. Last, one of the biggest challenges when measuring patient-reported outcomes is what instrument assesses HRQoL or other relevant topics best among the study population. Given the qualitative results of our data, the EORT-QLQ-C30 may be too generic to measure the impact of total interval length on HRQoL of sarcoma survivors. In future research, patient-reported outcome measures focussing on disability, distress, or recurrence may better capture this relationship.

Our study has resulted in more understanding of the survivorship experience. Perceived impact of the diagnostic interval and coping strategies have a long-lasting effect on global HRQoL and all functional scales, it thus seems important to keep the diagnostic trajectory and perception thereof as short as possible.

Since the perceived effect of diagnostic interval length still causes physical and psychological disabilities amongst patients 2-10 years after diagnosis, improvement of services, treatment and rehabilitation programs may contribute to improving HRQoL of sarcoma patients. Patients with maladaptive coping strategies are at risk of lower HRQoL. Sarcoma care could be improved if healthcare providers acknowledge patients' frustrations regarding their diagnostic pathway and have eye for their coping strategies. If necessary, supportive care focussing on coping strategies could be given early in the treatment pathway.

Conclusion

The perceived impact of diagnostic interval length was associated with HRQoL of sarcoma survivors, whereas actual length was not associated with HRQoL. Maladaptive coping strategies were independently associated with HRQoL. This offers opportunities for early intervention to improve HRQoL.

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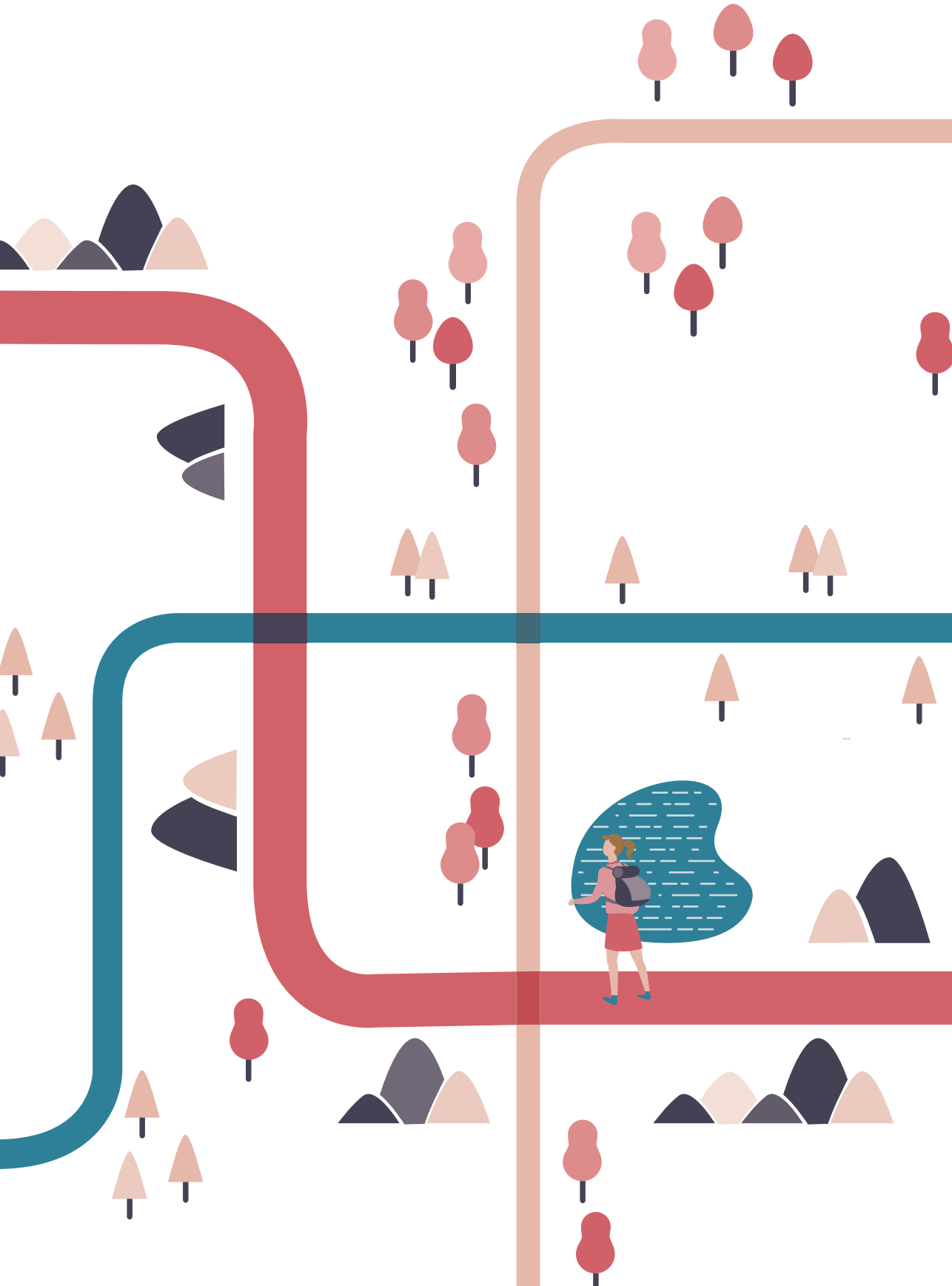

CHAPTER 6

The prolonged diagnostic pathway of young adults (aged 25-39) with cancer in the United Kingdom: results from the Young Adult Cancer Patient Journey Study

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Submitted

Abstract

Purpose

Teenagers and young adults (TYAs; aged 13-24) experience prolonged intervals to cancer diagnosis. Insight into diagnostic intervals in young adults (YAs; aged 25-39) and subgroups at risk for long intervals is lacking. We investigated the diagnostic pathway of YA cancer patients, examined patient and tumor characteristics associated with its length, and compared the patient interval length of our sample with a TYA cohort.

Methods

In this cross-sectional survey YAs diagnosed with cancer in the UK in the past five years completed a questionnaire describing their patient (time from first symptom to first doctor consultation) and healthcare interval (from first consultation until consultation with a cancer specialist), sociodemographic, and clinical characteristics. Associations between characteristics and interval length were examined and compared with previously published data in TYAs.

Results

Among 341 YAs the patient interval lasted ≥2 weeks, ≥1 month, and ≥3 months in 60%, 42%, and 21%, respectively, compared to 48%, 27%, and 12% in the TYA group. The healthcare interval lasted ≥2 weeks, ≥1 month, and ≥3 months in 62%, 40%, and 17% of YA patients, respectively. YAs with melanoma or cervical cancer were most likely to experience long intervals, whereas YAs with breast cancer and leukemia were most likely to experience short intervals.

Conclusion

Most YAs were not seen by a cancer specialist within 2 weeks of GP consultation. Interval lengths in YAs were associated with cancer diagnosis. Patient intervals were longer among YAs than among TYAs. Our study highlights long diagnostic pathways among YAs and calls for more awareness among healthcare professionals about malignancies in this age group.

Introduction

Cancer in adolescence and young adulthood (AYA), defined as patients aged 15-39 at cancer diagnosis, is uncommon, accounting for 5% of all cancer diagnoses[1]. Leukemia, lymphoma, testicular cancer, and thyroid cancer are the most common cancers among 15 to 24 year olds, while breast cancer and melanoma are most common among 25-39 year olds[2].

AYA cancer patients face unique developmental, physical, and psychosocial issues that make adjustment to their disease and health-maintenance challenging[3]. AYAs describe unsatisfactory care experiences such as lack of recognition of their autonomy by healthcare providers (HCPs), lack of peer support, and inappropriate care environments[4, 5]. To address these issues, the United Kingdom (UK) has rapidly expanded the availability of dedicated services for teenagers and young adults (TYA) ages 13 to 24. In contrast, no age-specific care services are available for young adult (YA) cancer patients aged 25 to 39 years.

Historically, progress in survival for AYAs has lagged behind both children and older adults, at least partly due to a prolonged diagnostic pathway[6-8]. Recently, we and others showed this gap in survival has closed for most, but not all tumors[9, 10]. Early diagnosis of cancer is key to facilitate the start of treatment and can improve psychosocial and clinical outcomes[11-13]. The cause of prolonged diagnosis among AYA is likely to be multifactorial[14, 15], and may include a lack of awareness amongst AYAs and HCPs, heterogenous and non-specific symptoms, and the rarity of cancer at this age. Reducing time to diagnosis is a key area for improving cancer care in the National Health Service[16]. The BRIGHTLIGHT study, assessing specialist care for TYAs with cancer in England[17], is the largest study among TYA patients looking at diagnostic timeliness[15]. In this study, over a quarter of participants (27%) waited more than one month to approach an HCP about symptoms[15].

Although age-specific guidelines to improve diagnostic timeliness in TYAs have been developed in the UK, for YAs, no specific guidance exists[18]. Information regarding YA's diagnostic pathway is lacking and often obscured in studies of older adults where most patient are over age 50. As life-events and the distribution of cancer types among YAs are distinct compared to older adults, available evidence cannot be extrapolated to YAs.

To improve healthcare services for YAs, we aim to describe the diagnostic pathway of patients aged 25-39 at diagnosis, identify factors associated with a prolonged pathway, compare the time from first symptom to doctor consultation in YAs with that in TYAs, and describe suggestions made by YAs to improve the diagnostic pathway.

Methods

Study design and participants

In this cross-sectional observational study, we invited all surviving patients diagnosed with cancer (ICD-10 codes C00-C97) aged 25-39 years treated at a participating trust (The Royal Marsden Hospital NHS Foundation Trust, East Suffolk and North Essex NHS Foundation Trust, University Hospital Southampton NHS Foundation Trust, Barts Health NHS Trust, Imperial College Healthcare NHS Trust, and East and North Hertfordshire NHS Trust). Patients were eligible if they were diagnosed in the last 5 years, able to communicate in English and could complete questionnaires independently. Patients with a previous cancer diagnosis were excluded.

Ethical approval

The Royal Marsden and Institute of Cancer Research Joint Committee on Clinical Research reviewed and sponsored the study (CCR4648). The Research Ethics Committee and Health Research Authority in the UK approved the study nationally (17/LO/0219).

Recruitment and data collection

Eligible patients received a letter from their treating physician explaining the purpose of the study. Patients provided informed consent before taking part. Data collection was conducted from May 2018 until March 2019 using PROFILES(www.profilesregistry.nl), a web-based system designed to collect patient-reported outcomes in cancer trials. Questionnaires could be completed online or upon request by pencil-and-paper.

Study measures

Whilst the study was primarily designed to examine unmet supportive care needs of YAs, this paper describes secondary analyses to explore the diagnostic pathway of participants.

Demographic and clinical variables

The questionnaire package contained socio-demographic items, including age at diagnosis, gender, ethnicity, relationship status, educational level, and gross income per annum. Patients also self-reported clinical data including tumor type and comorbidities.

Diagnostic pathway

The questionnaire package included a number of items about the diagnostic pathway, including items developed by the BRIGHTLIGHT group to assess the diagnostic pathway of TYAs[15, 19]. We explored the patient and healthcare intervals and the number of pre-diagnosis consultations as a surrogate marker of diagnostic timeliness (Figure 1). The patient interval, as defined previously[20], encompasses the time between the first symptom and first consultation with a HCP. The healthcare interval is the time from the

first HCP consultation until the first consultation with a cancer specialist. Interval items had categorical response options of under 1 week, 1-2 weeks, 2-4 weeks, 1-3 months, 3-6 months, 6-12 months, more than 12 months or 'I don't know'. The number of pre-diagnosis consultations was measured with response options 0, 1, 2-3, '4 times or more'.

º spoke to: "On a scale of 1 to 10, do you think your symptoms or concerns were taken seriously the first time you spoke to a doctor?". A single free-text question asked for patient opinions on appropriate ways to reduce the time from symptom presentation to diagnosis.

Statistical analysis

Descriptive statistics were reported for participants' demographic and clinical data, patient and healthcare interval lengths, the number of consultations and whether patients felt they were taken seriously. Mean and standard deviation are reported for continuous variables. Frequency and percentage are reported for categorical variables. For patient and healthcare intervals, we dichotomized interval lengths at three separate thresholds: <2 weeks versus ≥2 weeks, <1 month versus ≥1 month, and <3 months versus ≥3 months.

We performed univariate logistic regression analyses to detect associations between categorical independent variables and the length of the patient and healthcare intervals dichotomized at 1 month following previous studies[15, 21]. Odd ratios (OR) and 95%-confidence intervals (95% CI) are presented. Independent samples t-tests were performed for continuous variables. We did not perform multivariable analysis because there were too few observations in each cancer type.

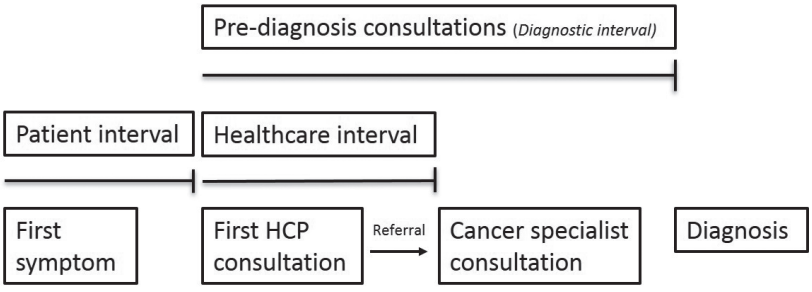

Figure 1 Diagnostic pathway

The number of pre-referral consultations is an indicator of diagnostic timeliness as patients experiencing more pre-referral consultations have longer intervals from symptom presentation to diagnosis[22]. We argue that two consultations are usually needed before referral, thus ≥4 consultations best reflect a prolonged interval. Therefore, we dichotomized diagnostic timeliness into <4 or ≥4 consultations. Fisher's exact tests were performed to test associations between categorical variables and the number of consultations before diagnosis.

To compare our results with TYA patient intervals, we used data published by the BRIGHTLIGHT study group[15]. We were unable to compare the healthcare interval or number of consultations, as definitions and cut-off points between the two cohorts differed. We grouped carcinomas and combined all germ-cell tumors to make direct comparisons with the BRIGHTLIGHT cohort. Groups with too few observations or not occurring in both cohorts were excluded from the analysis. We reported frequency and percentage of patient intervals in both groups and tested the differences using X^2 tests. As we had no access to the raw data from the BRIGHTLIGHT study, tests were limited to univariate analysis. Associations between patient characteristics and age group were restricted to single levels of patient. If the expected number within a cell was smaller than five, Fisher's exact tests were performed.

All missing data was assumed to be missing at random and only complete cases were analyzed. All statistical analyses were performed using IBM SPSS 25.0. Two-sided p-values of <0.05 were considered statistically significant.

Qualitative Analysis

We analyzed free-text responses using inductive coding followed by axial coding to group participants' answers[23]. Two investigators independently coded the data (VS and OH). We describe the number of times each recommendation occurred.

Results

Participants

Of the 1657 invited patients, 348 completed the questionnaire (response rate 21%); 341 participants had complete healthcare interval data and were included in the analysis. The mean age was 33.3 years, 108 (32%) were male, and 288 (84%) were white (Table 1A). Breast cancer and testicular cancer were the most common diagnoses. Mean time between diagnosis and questionnaire completion was 2.9 years (standard deviation 1.7).

Table 1A: Participant characteristics at time of survey

	All participants (N=341)
Age at diagnosis in years, mean (SD)	33.3 (4.3)
Gender	
• Male	108 (32)
• Female	233 (68)
Ethnic group	
• White	288 (84)
• Non-White	53(16)
Cancer diagnosis	
• Breast cancer	113 (33)
• Leukemia	9 (3)
• Lymphoma	27 (8)
• Sarcoma	22 (7)
• Testicular cancer	52 (15)
• Ovarian cancer	13 (4)
• Melanoma	8 (2)
• Thyroid cancer	20 (6)
• Colorectal cancer	14 (4)
• Cervical cancer	32 (9)
• Other	30 (9)
• Missing	1 (0)
Patient interval length	
(n=307; non-exclusive)	
• >2 weeks	185 (60)
• >1 month	129 (42)
• >3 months	63 (21)
Healthcare interval length	
(n=341; non-exclusive)	
• >2 weeks	210 (62)
• >1 month	135 (40)
• >3 months	59 (17)
Presence of symptom upon presentation	
• Symptomatic	320 (94)
• Asymptomatic	21 (6)
Relationship status	
• Single	58 (17)
• In a relationship	83 (24)
• Married / civil partnership	189 (55)
• Divorced	11 (3)
Educational level	
• No education or primary school	2 (1)
• Secondary school	32 (9)
• Vocational	14 (4)
• College	66 (19)
• University	201 (59)
• Other	26 (8)
gross income per annum	
• < £ 20 000	88 (26)
• £ 20 000-30 000	51 (15)
• > £ 30 000	162 (48)
• Missing	40 (12)

Table 1A: Continued

	All participants (N=341)
Comorbidities	
• 0	177 (52)
• 1	114 (33)
• ≥2	50 (15)

Patient interval

Patient interval data was completed by 307 participants. Seventy-eight percent first told a doctor about their symptoms, mostly their general practitioner (GP)(84%). A minority of patients were admitted as an emergency (4%) or were detected through screening (6%). Those detected through screening had breast (n=2) or cervical cancer (n=16). Half the participants with cervical cancer (n=16) were not detected through screening. The majority (68%) of patients felt they were taken seriously by the first doctor they spoke to.

Although 94% of participants experienced symptoms, the majority (60%) waited longer than two weeks before consulting a doctor. In 42% and 21% of cases, participants waited longer than one and three months, respectively (Table 1A). Reasons for delaying included waiting to see whether symptoms would disappear spontaneously, thinking there was no need to go to the doctor, being too busy, and not wanting to bother the doctor unnecessarily. Patients with melanoma and cervical cancer had significantly higher odds of experiencing a patient interval greater than one month compared to those with breast cancer (Figure 2A). Gender, age, and ethnicity were not associated with patient interval length (Table 1B).

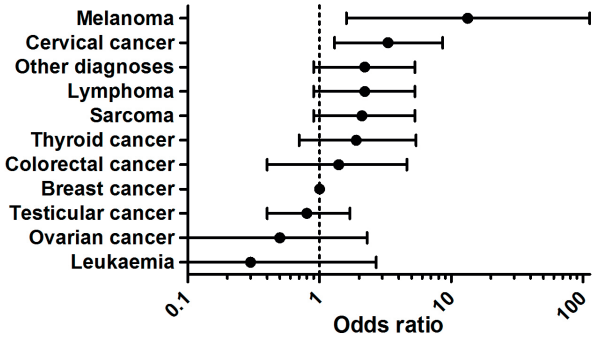

Figure 2A: Odds ratios of patient interval ≥1 month by diagnosis

Table 1B: Participant characteristics by interval length

	Patient interval (N=307)			Healthcare interval (N=341)		
	<1 month	≥1 month		<1 month	>1 month	
	Mean (SD)	Mean (SD)	P-value#	Mean (SD)	Mean (SD)	P-value#
Age at diagnosis in years	33.5 (4.3)	33.2 (4.4)	0.6	33.7 (4.2)	32.7 (4.3)	0.03
	N (%)	**N (%)**	**OR (95% CI)**	**N (%)**	**N (%)**	**OR (95% CI)**
All participants	178 (58)	129 (42)	NA	206 (60)	135 (40)	
Gender						
• Male	57 (55)	46 (45)	1 (ref)	68 (63)	40 (37)	1 (ref)
• Female	121 (59)	83 (41)	0.9 (0.5-1.4)	138 (59)	95 (41)	1.2 (0.7-1.9)
Ethnic group						
• White	149 (57)	111 (43)	1 (ref)	172 (60)	116 (40)	1 (ref)
• Non-White	29 (62)	18 (38)	0.8 (0.4-1.6)	34 (64)	19 (36)	0.8 (0.5-1.5)
Cancer diagnosis						
• Breast cancer	72 (66)	38 (34)	1 (ref)	95 (84)	18 (16)	1 (ref)
• Leukemia	6 (86)	1 (14)	0.3 (0.0-2.7)	8 (89)	1 (11)	1.1 (0.1-5.6)
• Lymphoma	12 (46)	14 (54)	2.2 (0.9-5.3)	9 (33)	18 (67)	10.6 (4.1-27.2)^
• Sarcoma	9 (47)	10 (53)	2.1 (0.9-5.3)	6 (27)	16 (73)	14.1 (4.9-40.8)^
• Testicular cancer	35 (70)	15 (30)	0.8 (0.4-1.7)	43 (83)	9 (17)	1.1 (0.5-2.7)
• Ovarian cancer	8 (80)	2 (20)	0.5 (0.1-2.3)	7 (54)	6 (46)	4.5 (1.4-15.0)^
• Melanoma	1 (12)	7 (88)	13.3 (1.6-111.8)^	3 (38)	5 (63)	8.8 (1.9-40.1)^
• Thyroid cancer	8 (50)	8 (50)	1.9 (0.7-5.4)	6 (30)	14 (70)	12.3 (4.2-36.3)^
• Colorectal cancer	7 (58)	5 (42)	1.4 (0.4-4.6)	3 (21)	11 (79)	19.4 (4.9-76.3)^
• Cervical cancer	8 (36)	14 (64)	3.3 (1.3-8.6)^	16 (50)	16 (50)	5.3 (2.2-12.4)^
• Other	12 (46)	12 (46)	2.2 (0.9-5.3)	10 (33)	20 (67)	10.6 (4.2-26.3)^
Presence of symptom upon presentation						
• Symptomatic	178 (58)	129 (42)	NA	190 (59)	130 (41)	1 (ref)
• Asymptomatic	NA	NA		16 (76)	5 (24)	0.5 (0.1-1.3)

#Independent samples t-test; NA = not applicable; ^p<0.0;. OR = odds ratio; CI = confidence interval

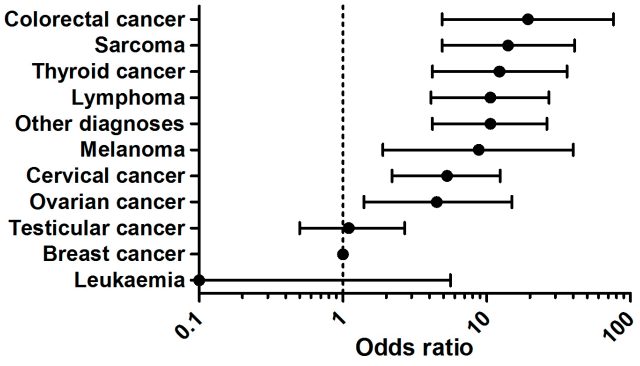

Figure 2B: Odds ratios of healthcare interval ≥1 month by diagnosis

Healthcare interval

Most patients (62%) had a healthcare interval ≧2 weeks. Forty percent of patient intervals were ≧1 month and 17% ≧3 months (Table 1A). Compared to breast cancer, all other cancer types except for leukemia and testicular cancer had significantly higher odds of experiencing a healthcare interval ≧1 month (Figure 2B). Gender, ethnicity and the presence of a symptom were not associated with healthcare interval length. Patients with an interval ≥1 month were significantly younger than patients with an interval <1 month(Table 1B).

Before receiving a diagnosis, 90% of patients spoke to their GP, 14% to an A&E doctor, 61% to a hospital doctor not in A&E, 9% to a walk-in center clinician, 2% to a polyclinic doctor, and 12% to another doctor. A considerable number of participants (13%) spoke to their GP or a hospital doctor other than in A&E (12%) ≥4 times before diagnosis (Figure 2C).

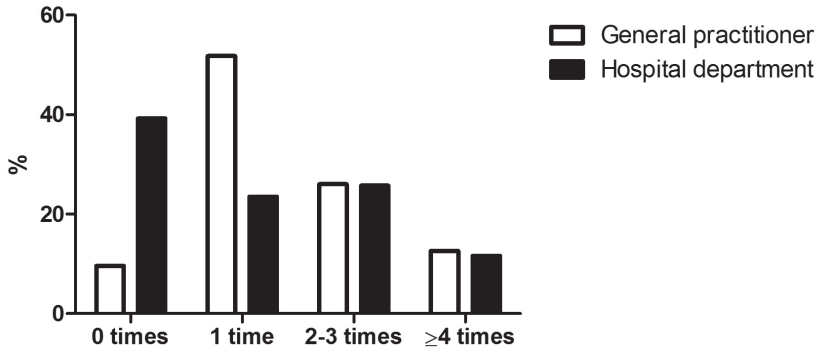

Figure 2C: Number of pre-diagnosis consultations

The number of consultations, regardless of location, was not associated with age, gender, or symptom presence (Table 1C). Cancer type was associated with ≥4 GP consultations and ≥4 hospital doctor consultations. Participants diagnosed with leukemia, sarcoma, ovarian cancer, thyroid cancer, colorectal cancer, and "other diagnoses" most often had ≥4 GP consultations. Participants diagnosed with leukemia, lymphoma, sarcoma, testicular cancer, ovarian cancer, and "other diagnoses" most often had ≥4 hospital doctor consultations.

Table 1C: Participant characteristics with 4 or more pre-diagnosis consultations

	≥4 GP consultations		≥4 hospital consultations	
	Mean (SD)		**Mean (SD)**	
Age at diagnosis in years	32.3 (4.5)#		33.0 (4.3)#	
	N (%)~	**p-value***	**N (%)~**	**p-value***
All participants	42 (13)		37 (12)	
Gender		0.593		0.349
• Male	11 (11)		14 (14)	
• Female	31 (14)		23 (11)	
Ethnic group		1.000		1.000
• White	36 (13)		31 (12)	
• Non-White	6 (12)		6 (12)	
Cancer diagnosis		0.006**		0.000**
• Breast cancer	5 (5)		3 (3)	
• Leukemia	2 (25)		4 (50)	
• Lymphoma	4 (15)		7 (27)	
• Sarcoma	5 (23)		3 (14)	
• Testicular cancer	2 (4)		6 (12)	
• Ovarian cancer	3 (23)		2 (15)	
• Melanoma	1 (13)		0 (0)	
• Thyroid cancer	5 (25)		2 (11)	
• Colorectal cancer	4 (29)		1 (7)	
• Cervical cancer	4 (13)		2 (7)	
• Other	7 (25)		7 (29)	
Presence of symptoms at presentation, n(%)		1.000		0.706
• Symptomatic	40 (13)		36 (12)	
• Asymptomatic	2 (11)		1 (6)	

~Percentages do not add up to 100% as data per column is arranged as proportion of patients with certain characteristics within a certain time interval. *Fisher's exact test; ** X^2 test. #Independent samples t-test showed no differences between age and number of consultations.

Comparison of findings with TYA population

The BRIGHTLIGHT cohort included 830 TYAs aged 12-24 at primary cancer diagnosis[15]. Their median age was 20 years, 55% were male, and 88% were white. Participants were diagnosed with lymphoma (32%), germ-cell tumors (19%), leukemia (13%), non-skin carcinomas (12%), bone cancer (10%), soft tissue sarcomas (6%), central nervous system neoplasms (4%), melanoma and skin carcinoma (4%), and unspecified (1%)(Table 2A).

Complete patient interval data was reported for 748 TYAs. Compared to 341 YA participants, 48% versus 60% had a patient interval ≥2 weeks, 27% versus 42% ≥1 month, and 12% versus 21% ≥3 months, for TYA versus YA patients, respectively (Figure 3).

Among males, white respondents and patients with lymphoma, YAs were significantly more likely to have a patient interval ≥1 month than TYA participants (Table 2B). YAs were

also significantly more likely to have a ≥2 week patient interval compared to TYAs among males and white patients, though this association was not significant among cancer diagnosis groups (Supplementary material A). When dichotomized at three months, YAs were significantly more likely to have a longer patient interval than TYA participants among males, white patients, or those diagnosed with lymphoma or sarcoma (Supplementary material A).

Table 2A: Characteristics of TYA and YA population

	TYA 12-24 years	YA 25-39 years
	N (%)	N (%)
All participants	748 (100)	307 (100)
Gender		
• Male	419 (56)	103 (34)
• Female	329 (44)	204 (66)
Ethnic group		
• White	657 (88)	260 (85)
• Non-White	91 (12)	47 (15)
Cancer diagnosis		
• Leukemia	89 (12)	7 (2)
• Lymphoma	248 (33)	26 (9)
• Soft tissue sarcoma	41 (5)	19 (6)
• Germ cell tumors	147 (20)	52 (17)
• Melanoma	28 (4)	8 (3)
• Carcinomas	87 (12)	152 (50)

TYA= teenagers and young adults; YA = young adults.

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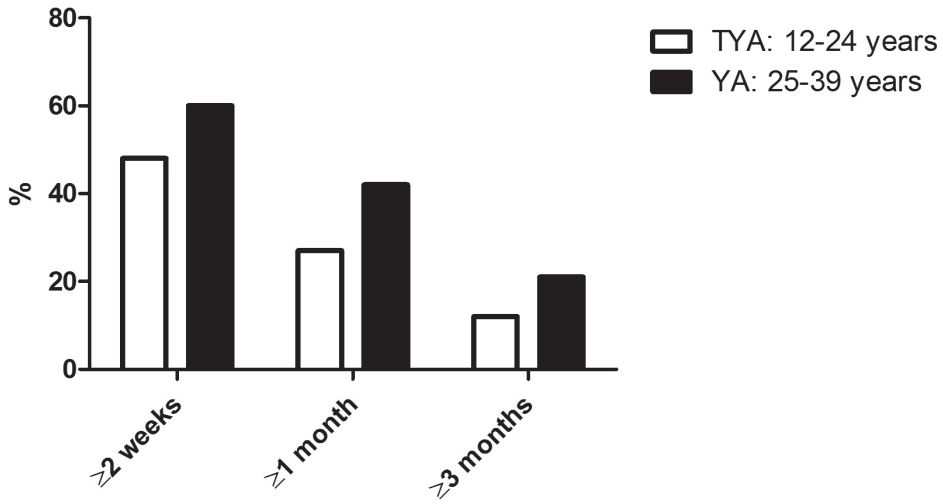

Figure 3: Proportion of participants by patient and interval length

Table 2B: Comparison of patient interval of TYA population with YA population

	TYA (N=748)		YA (N=307)		TYA vs YA
	<1 month	>1 month	<1 month	>1 month	>1 month
	N (%)	N (%)	N (%)	N (%)	X^2 p-value
All participants	544 (73)	204 (27)	178 (58)	129 (42)	-
Gender					
• Male	641 (74)	107 (26)	57 (55)	46 (45)	0.00
• Female	651 (71)	97 (29)	121 (59)	83 (41)	0.12
Ethnic group					
• White	566 (72)	182 (28)	149 (57)	111 (43)	0.00
• Non-White	726 (76)	22 (24)	29 (62)	18 (38)	0.21
Cancer diagnosis					
• Leukemia	726 (75)	22 (25)	6 (86)	1 (14)	0.36
• Lymphoma	682 (73)	66 (27)	12 (46)	14 (54)	0.01
• Soft tissue sarcoma	735 (68)	13 (32)	9 (47)	10 (53)	0.28
• Germ cell tumors	712 (76)	36 (24)	37 (71)	15 (29)	0.69
• Melanoma	734 (50)	14 (50)	1 (13)	7 (88)	0.06
• Carcinomas	720 (68)	28 (32)	93 (61)	59 (39)	0.66

TYA= teenagers and young adults; YA = young adults.

Suggestions for improving the diagnostic pathway

Many patients (39%) gave a total of 191 suggestions to improve the diagnostic pathway. Themes included raising awareness of cancer in YAs and taking young people seriously, communication, and reducing passive waiting times. Table 3 shows exemplary quotes.

The majority (39%) of recommendations were about raising awareness among HCPs and YAs that age should not preclude cancer and taking YAs seriously (Table 3). Nearly a quarter (21%) suggested better communication, such as providing more information about investigations, not skirting around cancer suspicions, and not giving false reassurance. One in six (16%) thought the healthcare interval length could be reduced by shortening wait times for examinations, referrals and appointments, and sharing more information between institutions and departments.

A small number of remarks were about the patient interval, recommending that YAs should not wait to contact their GP with abnormalities and be persistent about getting a diagnosis (9%).

There were no major differences between groups, but participants with a healthcare interval ≥1 month more often remarked about raising awareness and being taken seriously (57%), and reducing waiting times for examinations, referrals, and appointments (50%).

Table 3: Quotes supporting qualitative analyses

Raising awareness and taking young people seriously	*"I didn't come across many well-informed doctors before I was admitted to the ***. I think cancer was dismissed as a possible reason because I was relatively young and otherwise fit and healthy. No one took my tumor markers despite me having lumps/swelling. Perhaps my only suggestion is raising awareness with all doctors that age is not a reason to discount cancer if they can't immediately identify the cause of a symptom. A blood test may have cut down my wait significantly."*
	"I rarely felt like I was being listened to and taken seriously as an individual who knew their own body. The GP only took me seriously when I found that a pre-existing lump in my breast had grown almost overnight, by which time it was too late. My sense was that the emergency/rapid response care was very good; but the preventative care and taking a holistic look at my symptoms in the early stages was completely overlooked."
Communication	*"I didn't realize they could tell you on the day that its cancerous, I thought you had to wait for the results, so I was very unprepared and alone (without my husband/ parent)."*
	"My consultant sent me for a fine needle aspiration but told me this was fairly routine. I was not told this was a test for cancer. I feel that I should have been given at least some mild warning of the possibility of cancer by the consultant."
Reducing passive waiting times	*"Reducing the wait between being referred to seeing a specialist or having tests. It's a very stressful and scary time."*
	"Share test results/scan info between trusts so tests do not have to repeated."

Discussion

In this study we investigated the diagnostic pathway of YA cancer patients, examined patient and tumor characteristics associated with the length of the diagnostic pathway, compared the patient interval length of our sample with a TYA cohort, and reported patients' suggestions for improving the diagnostic pathway.

Both patient and healthcare intervals were long among a substantial proportion of participants. Forty-two percent of participants had patient intervals ≥1 month and 21% ≥3 months. Healthcare intervals were ≥1month for 40% and ≥3 months for 17% of participants. Gender and ethnicity were not associated with diagnostic intervals or number of consultations before diagnosis. Age was only associated with the healthcare interval, where age was slightly lower among patients with a ≥1 month interval. Remarkably, symptom presence at diagnosis did not influence healthcare interval length nor the number of GP or hospital doctor consultations.

Subtype specific cancer diagnosis was associated with both patient and healthcare interval length and number of pre-diagnosis consultations. YAs with melanoma were most likely to wait ≥1 month before consulting a doctor, but never had ≥4 hospital doctor consultations, as expected with identifiable presenting symptoms (an itching or bleeding pigmented lesion) of this cancer. The finding that identifiable presenting symptoms may lead to a short patient interval is supported by a sub analyses of the BRIGHTLIGHT cohort, which shows 38% of participants with mole changes had a patient interval >1month[24].

YAs with cervical cancer were more likely to wait ≥1 month as well, and some had ≥4 GP consultations. Notably, half of these patients were not detected through screening. However, in the NHS one in four women skip cervical screening, with the proportion increasing to one in three among those aged 25 to 29[25]. Unfortunately, our study did not ask cervical cancer patients not detected through screening whether they participated in the screening program. We therefore cannot conclude whether these were interval carcinomas occurring between two screening dates.

In breast cancer, one might expect a short patient interval as breast cancer patients form a distinct group compared to other cancer patients, given the general knowledge about the disease and its symptoms in the population. However, a third waited more than one month before consulting a doctor. We hypothesize this may be due to YAs having busy lives and not recognizing symptoms as caused by malignancy. Two participants with breast cancer reported being diagnosed through screening, possibly in a screening program for a hereditary cancer syndrome. The standard NHS screening program for breast cancer

starts at age 50. Regarding the breast cancer healthcare interval, it is unsurprising that few participants had ≥4 GP (5%) or hospital (3%) consultations.

The NICE two-week-wait rule (TWW) states patients with a suspicion of cancer should be referred to a specialist in two weeks and additional investigations, including biopsies, should be carried out on one day[26]. Therefore, one would expect the healthcare interval to be shorter than two weeks for most participants. However, the healthcare interval lasted ≥2 weeks in 43% of YAs, and ≥1 month in 16%. As expected, few had a healthcare interval ≥3 months (2%). It is known that younger patients present less often via the TWW, and more often via non-TWW referrals or in emergency presentations, however, this may not be directly correlated with the healthcare interval, as the majority of patients will be diagnosed through emergency presentation[27].

Participants with diagnoses other than breast cancer were more likely to experience a healthcare interval ≥1 month. The only exception was leukemia, though these patients had many pre-diagnosis GP and hospital consultations. The need to perform additional investigations in leukemia patients to confirm the diagnosis may explain the high number, but most of these investigations can be undertaken and interpreted relatively quickly. Alternatively, patients with leukemia often present as an emergency, although this percentage is higher in TYAs than YAs[27].
Comparison with existing literature is difficult, as studies focusing solely on YAs 25-39 years of age are rare. This study enabled a direct comparison of YA and TYA patient intervals with findings from the BRIGHTLIGHT study. This showed that YAs in our study in general had longer patient intervals. Age-related factors may contribute to this difference, such as differing life-priorities (e.g. having a job, taking care of children). The distribution of diagnoses may play an important role as well: the proportion of participants diagnosed with leukemia and lymphoma was larger in the TYA group, whereas carcinomas were diagnosed more often in the YA group. Participants who were male or white were more at risk of a longer patient interval when aged 25-39, compared to those aged 12-24. Furthermore, those diagnosed with lymphoma with a patient interval ≥1 month, or ≥3 months, were also more likely to be older. This was also true for patients with soft tissue sarcoma who had a patient interval ≥3 months. These findings are relevant and call for actions to increase awareness among YAs to reduce the patient interval.

Our findings support those of an American study with patients aged 15-29 that found cancer diagnosis was significantly associated with interval length, whereas ethnicity, age, and gender were not[28]. Similarly, a National Cancer Intelligence Network report found that cancer diagnosis played a major role in determining how TYAs were likely to be referred[27].

A Danish study amongst AYAs (aged 15-39) reported GP consultations increased several months before cancer diagnosis, possibly reflecting low awareness of patients and HCPs that symptoms may be due to malignancy[29].

Although 68% of participants felt they were taken seriously in their first consultation, most suggestions to improve the diagnostic pathway were about taking YAs seriously, and not rejecting cancer as a possibility due to age. Additional recommendations were made about communication, and reducing passive waiting time, e.g. for additional examinations, referrals, or requesting information from other institutions. There were no major differences by interval length and most recommendations were not age specific.

To our knowledge, this is the first study to examine the diagnostic pathway of YA cancer patients, with various cancer diagnoses. However, this study has several limitations. First, intervals and the number of consultations were self-reported, potentially introducing recall bias. A generally consistent finding is that as the recall time increases, the ability to recall events degrades[30]. However, significant events, such as a cancer diagnosis, are less likely to be forgotten[30]. Furthermore, estimating the duration of an event is extremely stable[31]. To minimize the effect of recall bias, patients were asked to report the duration of intervals instead of dates, and questions were anchored to a life event (the cancer diagnosis).
Second, the study may be subject to selection bias as only 21% of invited participants responded.

Third, the distribution of tumors does not accurately reflect the incidence of cancers in YAs in the population[10]. For males, the most common cancers among YAs in the UK are testicular cancer, melanoma, and gastro-intestinal tumors. For females these are breast cancer, melanoma, and tumors of the genito-urinary tract. Lymphoma and sarcoma are therefore overrepresented in our study, whilst melanoma and gastro-intestinal tumor may be underrepresented. We invited patients from hospitals in the South East, East, and London regions, who may have relatively more TWW referrals than those diagnosed in the North East[27]. Interval length may be underestimated when compared to the whole of England. Lastly, as subgroups were small, we were unable to perform adjusted analyses and the results should therefore be interpreted with caution.

Our findings highlight that cancer is still seen as a disease of the elderly. We recommend increasing awareness and gain better insight in the diagnostic pathway of patients aged 25-39 and raise awareness in the general public and among health care professionals to shorten time to diagnoses. Further research with a larger population is needed to confirm our findings with respect to identified risk groups, and to study the impact of a prolonged diagnostic pathway on clinical and patient-reported outcomes for YAs.

Conclusion

Patient and healthcare interval length is long in a substantial proportion of YA cancer patients. Diagnostic intervals were associated with cancer diagnosis, with YAs with melanoma or cervical cancer experiencing a long time to diagnosis, and YAs with breast cancer and leukemia experiencing a short diagnostic pathway. Compared to the TYA population, YA patients who were male, white, or diagnosed with lymphoma or STS, were more likely to experience a prolonged patient interval. Participants recommended improving the diagnostic pathway by raising awareness, enhancing communication, and reducing passive waiting time. The diagnostic pathway of YAs should be studied further and awareness about cancer in this age group should be increased.

Supplementary material A: comparison of patient interval of TYA population with YA population

	TYA ≥2 weeks	YA ≥2 weeks	TYA ≥3 months	YA ≥3 months
All participants, n(%)	359 (48)	185 (60)	91 (12)	63 (21)
Gender, n(%)#				
• Male	195 (54)**	64 (35)**	48 (53)**	22 (35)**
• Female	164 (46)	121 (65)	43 (47)	41 (65)
Ethnic group, n(%)#				
• White	321 (89)**	161 (87)**	84 (92)**	57 (90)**
• Non-White	38 (11)	24 (13)	7 (8)	6 (10)
Cancer diagnosis, n(%)#				
• Leukaemia	42 (12)	4 (2)	5 (5)	0 (0)
• Lymphoma	125 (35)	17 (9)	33 (36)**	10 (16)**
• Soft tissue sarcoma*	17 (5)	13 (7)	4 (4)**	8 (13)**
• Testicular cancer**	66 (18)	25 (14)	17 (19)	5 (8)
• Melanoma	19 (5)	8 (4)	10 (11)	1 (2)
• Carcinoma	43 (12)	86 (47)	13 (14)	29 (47)

*Soft tissue sarcoma of YA population contained 1 Ewing sarcoma. **p<0.005.

#Percentages are row percentages.

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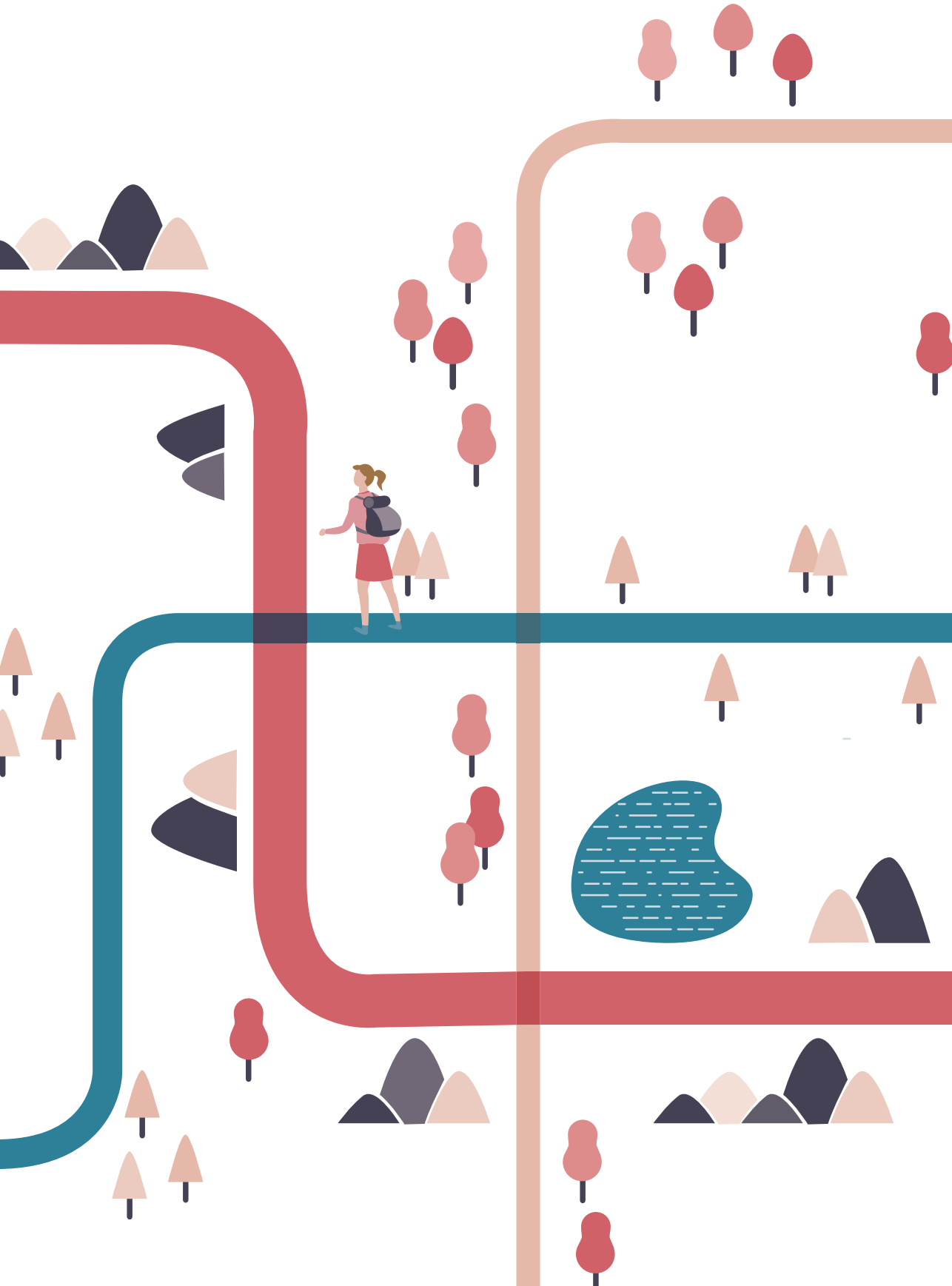

CHAPTER 7

QUality of life and Experiences of Sarcoma Trajectories (the QUEST study): protocol for an international observational cohort study on diagnostic pathways of sarcoma patients

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Abstract

Introduction

Sarcomas are rare tumours with considerable heterogeneity. Early and accurate diagnosis is important to optimise patient outcomes in terms of local disease control, overall survival (OS) and health-related quality of life (HRQoL). Time to diagnosis is variable in bone as well as soft tissue sarcoma. Possible factors for a long time from first symptom to diagnosis (the total interval) include patient, tumour, and healthcare characteristics, but until now the most relevant risk factors and its association with outcomes remain unknown.

Our study aims to (1) quantify total interval, the time interval from first symptom until (histological) diagnosis; (2) identify factors associated with interval length, and (3) determine the association between total interval and HRQoL, stage and tumour size at diagnosis, progression-free survival (PFS), and OS.

Methods and analysis

We will conduct a longitudinal, prospective, international, multicentre cohort study among patients aged ≥18 with newly diagnosed bone or soft tissue sarcoma at eight centres (three in United Kingdom, five in The Netherlands). Patients will be asked to complete questionnaires at five points in time; one at diagnosis and at follow-up points of 3, 6, 12, and 24 months. Questionnaire data is collected within the PROFILES registry: an international data management system for collection of patient-reported outcomes. Clinical data will be extracted from patient records. The primary endpoint is HRQoL at diagnosis, measured with the EORTC QLQ-C30. Secondary endpoints are stage and tumour size at diagnosis, PFS, OS, additional patient-reported outcomes, such as quality-adjusted life years and psychological distress.

Introduction

Sarcomas are a group of solid mesenchymal tumours, which comprise more than 70 histological subtypes, with considerable heterogeneity with respect to age at diagnosis, location, biological behaviour and outcome[1]. Approximately 80% of sarcomas are soft tissue sarcomas (STS), the remainder are bone sarcomas (BS). Sarcomas are typical examples of so-called rare cancers, with an estimated European incidence of 4-5 per 100 000 per year when taken all together[2], accounting for 1% of adult solid malignant cancers[3]. Patients with rare cancers have a higher mortality rate than those with common cancers, due to delays in diagnosis, suboptimal or inadequate treatment, fewer developments in novel therapies and opportunities to participate in clinical trials[4].

Early and accurate diagnosis of cancer is important to optimise patient outcomes in terms of local disease control, overall survival (OS) and health-related quality of life (HRQoL)[5, 6]. However, because of the heterogeneity and rarity of sarcomas, there is a lack of public awareness, limited experience of primary and secondary healthcare professionals, and absence of a typical presentation, resulting in late referrals to specialist sarcoma centres and prolonged time to diagnosis[7].

Time to diagnosis can be defined according to the research framework from Olesen et al, which we adapted to the situation as applicable for sarcomas[8-10]. The time between first symptom and (histological) diagnosis, is known as the total interval. This includes a patient and diagnostic interval, defined as time between onset of symptoms until consultation of a healthcare professional, and time between consultation of a healthcare professional and diagnosis, respectively. The latter can be further divided into a primary, secondary, and tertiary care interval, each of which refers to first consultation until referral to the next caregiver or diagnosis.

Possible risk factors for a prolonged total interval could be patient, tumour, or healthcare system characteristics. In order to study the latter, it is informative to compare patients from different countries. In both the Netherlands and United Kingdom (UK), general practitioners (GP) have an important role as healthcare gatekeepers. In general, people consult their GP who then decides whether referral is warranted and determines the acuteness and location of the referral. In the UK, privately insured patients can also self-refer to a hospital without seeing a GP. Furthermore, within the UK, a considerable amount of cancer patients is diagnosed at an emergency department, associated with worse outcomes[11]. Sarcoma care is formally centralized within the UK, whereas the Netherlands has bone sarcoma centres, and referral to dedicated STS centres is encouraged, but not commissioned. Furthermore, cultural differences may play a role in patient behaviour.

Also, longer travel time to a sarcoma centre in the UK compared to the Netherlands, may also affect total interval length.

Up to now, only few studies regarding total interval length and clinical outcomes in sarcoma have been published, most were retrospective and included mainly children. Some studies found that a longer total interval worsened OS, whilst others did not find inferior clinical outcomes[10]. Researchers have argued that this lack of an association, often referred to as the 'waiting-time paradox', may be because the studies have not been able to adequately adjust for the aggressiveness of the cancer tumours. The most significant effect of a long interval for sarcomas seems to be the increasing size of the lesion[12], with consequent decreased chance of uncomplicated resection with clear surgical margins, a greater risk of amputation, and increased risk of developing metastases[13]. This may also affect patient-reported outcomes such as health-related quality of life of sarcoma patients.

Health-related quality of life (HRQoL) is the patients' perception of his overall health in relation to physical, psychological and social aspects in life[14]. Three systematic reviews have been published on HRQoL of sarcoma patients, however, none of these looked at the association of total interval length and HRQoL[15-17]. In other cancers and chronic diseases, lengthening of total interval was associated with decreased HRQoL[18, 19]. HRQoL is an interesting outcome parameter for evaluating consequences of long total interval length and provides an insight into the patient's experience of the consequences of diagnostic delay. In addition to using patient-reported outcomes as a measure for quality of care, HRQoL can be used to conduct cost-utility analysis to estimate the ratio between the cost of a prolonged total interval, and the benefit of earlier diagnosis in terms of life-years (QALY).

Until now, risk factors for a long total interval in adult sarcoma care, as well as its effect on clinical and patient-reported outcomes remain unknown. These need to be studied in well-designed, large, prospective studies in order to prioritize interventions to optimize the total interval. Our study aims to quantify total interval, identify independent variables associated with a long interval (such as demographic and clinical factors), and determine the association between total interval and other dependent variables, such as HRQoL, stage and tumour size at diagnosis, progression-free survival (PFS), and OS (Figure1).

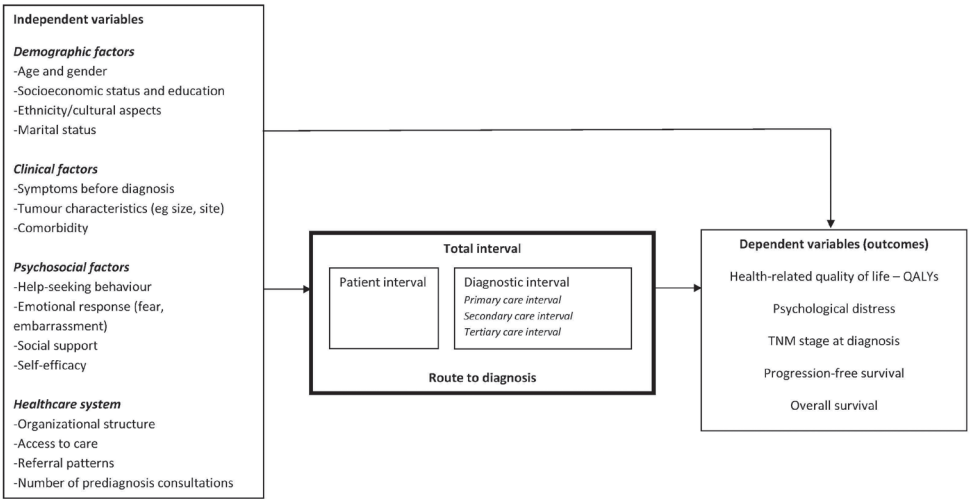

Figure 1: Schematic representation of study objectives

Methods and analysis

Study design and setting

We will conduct a longitudinal, prospective, cohort study among adult sarcoma patients, newly diagnosed in one of the participating study centres (5 centres in the Netherlands: Radboud University Medical Centre Nijmegen, Erasmus Medical Centre Rotterdam, University Medical Centre Leiden, University Medical Centre Groningen, Netherlands Cancer Institute Amsterdam; 3 centres in the UK: The Royal Marsden London, Christie Manchester, Royal Orthopaedic Hospital Birmingham, all NHS Foundation Trusts). The study started recruitment at the first centre in the Netherlands in February 2018, and in the UK in October 2018, and is currently recruiting.

After informed consent, patients are being asked to complete questionnaires at five points in time: the first at baseline, preferably before start of treatment or within four weeks thereafter, and at 3, 6, 12, and 24 months follow-up(Table 1). Baseline questionnaire completion will take about 45 minutes, follow-up questionnaires will take 20-30 minutes each.

Patient and public involvement

The different patient-reported outcome measures (PROMS) were selected in consultation with patient advocates. The Sarcoma Patients EuroNet, an international network of patient advocacy groups, has formulated research priorities, at least two of which will be addressed by our study: (1) earlier diagnosis and (2) patient-reported outcomes such

as health-related quality of life[20]. The questionnaire was pilot tested by patients, for acceptability and understandability. Study documents were reviewed by the patients who are members of the Royal Marsden Hospital Patient and Public involvement panel, and the ethics committee of Radboudumc. The panel and committee provided feedback on the protocol, questionnaires, patient information sheet and informed consent form, regarding content and readability, and changes were incorporated in the final documents. Patients have been and will be involved in study related presentations and publications.

Participants

Eligible patients are invited by their treating physician or a member of the research team. Inclusion criteria are: (1) aged ≥18; (2) new histological diagnosis of sarcoma as confirmed by a sarcoma histopathologist (according to ICD-10-GM codes C40 and C41 for bone sarcoma and C49 for soft-tissue sarcoma); (3) able to communicate in English or Dutch and to complete questionnaires themselves; (4) mental capacity to provide informed consent and participate in the study (as determined by the healthcare professional); and (5) diagnosed at or refered to one of the participating hospitals. Exclusion criteria are: (1) too ill to complete questionnaires (according to treating physician - patients who experience symptoms of are still egligble); (2) desmoid fibromatosis and gastrointestinal stromal tumours due to the different nature of the diseases (ICD-10-GM codes C15-20, C26, C48 and C80).

Data collection

Eligible patients receive a patient information sheet, which explains the goals and procedure of the study. It includes a link to a secure website (www.profielstudie.nl for both English and Dutch patients), a login name, and a password. After logging in, patients can provide informed consent and complete questionnaires online. Patients without access to internet or preference of written communication, receive a paper version of the informed consent form and questionnaire. Questionnaires completed on paper will be entered via the data entry option into the PROFILES system (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship; www.profilesregistry.nl [21]) by a member of the study team. The data entry portal has the same format as the online questionnaire data, minimizing the chance of errors and enhancing data extraction. Paper questionnaires will be stored in a secured room at study coordinating sites (Radboudumc and Royal Marsden Hospital). PROFILES is a data management system, set up in 2009 in the Netherlands for the study of physical and psychosocial impact of cancer and its treatment. The data collected in PROFILES is stored on a secure server in the Netherlands. In order to retrieve the data, an authorised member of the study team can login and download an SPSS or Excel file containing the encoded questionnaire data. PROFILES has been developed to the requirements of the higher education and research community and allows end to end encryption.

The research coordinator has access to a password protected file which links patients' study numbers to their electronical patient record number. Clinical data and survival data will be retrieved from the patients' medical record by a member of the study team into the electronic case report forms (eCRF) database (MACRO) which is maintained according to current norms and ICH-GCP standards, and is password protected. Patient records will not leave the hospital.

Finally, questionnaire data will be linked with the eCRF database (all encoded data) using study numbers. The combined dataset will be stored under appropriate password protection. Data will be recorded and retained in accordance with the Data Protection Act 1998.

Case report forms

CRFs will be completed at five time points during the study. The first will be completed upon inclusion, the following time points coincide with completion of follow-up questionnaires. The last CRF is also the end-of-study CRF which can be completed before 24 months if a patient withdraws or deceases. The information collected on the CRF will be stored on a secure CRF database using anonymous study numbers. Data collected includes documentation of eligibility criteria, date of diagnosis, tumour characteristics such as histology, TNM stage, tumour size, treatment regiment, re-occurrence of disease or metastases, reason for withdrawal of the study, and time of death, if applicable.

Questionnaires

We have combined self-designed questions and several validated questionnaires designed by other researchers (details below). For non-commercial scientific use no formal licenses are needed for the use of these questionnaires. Self-designed items and existent questionnaires not available in both English and Dutch, were translated with formal forward-backward translation by bilingual speakers. Table 1 summarizes the time-points at which each construct is being measured.

Socio-demographics

The questionnaires contain questions on socio-demographic characteristics of the participant at time of questionnaire completion, such as marital status and educational level. Co-morbidity is being measured with the self-administered co-morbidity questionnaire (SCQ), which is a validated list where patients report their co-morbidity during the past year[22].

Total interval

A 42-item list was self-designed to assess the total interval. Examples of questions are: " With which symptom(s), caused by the sarcoma, did you first go to a doctor?", "To which doctor did you first talk about your symptoms?", and "How often did you talk to the following doctors about your symptoms belonging to sarcoma, before you heard you had a sarcoma?". At follow-up, a few questions are repeated to complete data collection. We will sample survey the reported dates by cross-checking them with the patient's record. If more than 5% of the cross-checked dates deviates more than 1 month from the registered dates in the medical record, we will cross-check all dates and use the clinical reported dates for statistical analysis.

Health literacy

Health literacy is being assessed by a Dutch adaptation of Chew's Set of Brief Screening Questions (SBSQ) in a single item question[23-25].

Social support

Social support is being assessed by one single item: "Was the amount of support you received from others sufficient?" extracted from the Quality of Life-Cancer Survivors questionnaire[26, 27].

Self-efficacy

Self-efficacy is measured with the general self-efficacy scale (GSE)[28]. This 10-item scale assesses a general sense of perceived self-efficacy with the aim to predict coping with daily hassles as well as adaptation after experiencing a stressful life event. Self-efficacy is the belief that one can perform a novel or difficult task, or cope with adversity. Perceived self-efficacy facilitates goal-setting, effort investment, persistence in face of barriers and recovery from setbacks. Responses are made on a 4-point scale. A higher final composite score correlates with higher perceived self-efficacy.

Coping

Coping is assessed in the 3 months questionnaire with the help of the brief COPE[29]. Coping is about emotional and mental reactions, which enable people to activate sources of help, needed to cope with stress and problems. This 28-item scale measures 14 positive and negative styles of coping on a 5-point Likert-scale.

Resilience

Resilience is measured in the 6 months questionnaire using the brief resilience scale (BRS) [30]. Resilience is a skill which helps people recover from a life event. People with high (perceived) resilience can move on faster after a setback. The BRS is a 6-item scale with a 5-point Likert-scale.

HRQoL

HRQoL is being assessed with the EORTC QLQ-C30, version 3.0, which is validated and available in English and Dutch[31].This 30-item HRQoL questionnaire consists of five functional scales (physical, role, cognitive, emotional and social), a global quality of life scale, 3 symptom scales (fatigue, pain, nausea and vomiting), and a number of single items assessing common symptoms (dyspnoea, loss of appetite, sleep disturbance, constipation and diarrhoea) and perceived financial impact of the disease. After linear transformation, all scales and single item measures have scores ranging from 0-100. A higher score on the functional scales and global QoL means better functioning and HRQoL, whereas a higher score on the symptom scales means more complaints.

QALY

QALY is being measured with the EuroQol EQ-5D-5L, which is a descriptive system for the measurement of health[32]. It measures HRQoL on five dimensions: mobility, self-care, usual activities, pain-discomfort, and anxiety-depression. To make the EQ-5D-5L suitable for use in economic evaluations, the health status needs to be valued with a preference-elicitation method[33]. Both Dutch and English national values were collected and subsequently modelled[34, 35].

Psychological distress

Psychological distress is being assessed with the Hospital Anxiety and Depression Scale (HADS), which is validated in Dutch and English[36]. This 14-item instrument measures psychological distress, with 7 items each assessing anxiety and depression. The summed total score of the HADS will be used to reflect psychological distress. Higher total scores are indicative for more psychological distress.

Financial impact

We self-designed a 20-item questionnaire regarding financial barriers to care. The questions were designed based on a literature study of items that are important in health-seeking behaviour but have not been validated. Topics covered are financial barriers to care, financial impact of living with cancer, personal expenses, and potential solutions for reducing financial impacts.

Information provision

Five self-designed questions with multiple items are being asked to identify time-points and subjects on which participants would like more information.

Quality of care

Quality of care is being assessed with the 18-item Patient Satisfaction Questionnaire (PSQ-18)[37], available in both English and Dutch[38, 39]. This instrument yields scores

for each of seven different subscales: general satisfaction, technical quality, interpersonal manner, communication, financial aspects, time spent with doctor and accessibility and convenience. High scores reflect satisfaction with medical care. In addition, 3-5 self-designed single items to assess overall satisfaction of care at the primary doctor's office, hospital and sarcoma centre are being asked.

Endpoints

The primary endpoint is HRQoL of sarcoma patients at diagnosis (baseline) as measured with the EORTC QLQ-C30 (global health status). Secondary endpoints are: QALY, psychological distress, stage and tumour size at diagnosis, PFS, and OS.

If subgroups are large enough, we will conduct these analyses for different clinically relevant subgroups, such as different histological subtypes, geographical areas etc.

Table 1: time points and questionnaire items

Item (number of items)	Scale	0 months	3 months	6 months	12 months	24 months
Characteristics						
Socio-demographic (max 20)		X	X	X	X	X
Co-morbidity (15)	SCQ	X			X	X
Total interval (max 42)	Own design	X	X	X	X	X
Health literacy (1)	SBSQ	X				
Social support (1)	QLCS	X		X		X
Self-efficacy (10)	GSE	X				
Coping (28)	Brief COPE		X			
Resilience (6)	BRS			X		
Outcomes						
Health-related quality of life (30)	EORTC-QLQ-C30 version 3.0	X	X	X	X	X
Quality adjusted life years (6)	EQ5D5L	X	X	X	X	X
Psychological distress (14)	HADS	X	X	X	X	X
Financial impact (20)	Own design	X	X	X	X	X
Information provision (max 26)	Profiles registry		X			
Quality of care (max 23)	PSQ-18 and 3-5 single items	X	X	X	X	X
Total number of items		194	158	105	113	114

SCQ: Self-administered co-morbidity questionnaire; SBSQ: Set of Brief Screening Questions; QLCS: Quality of Life-Cancer Survivors; GSE: General self- efficacy; BRS: Brief Resilience Scale; HADS: Hospital Anxiety and Depression Scale; PSQ: Patient Satisfaction Questionnaire.

Sample size calculation

We expect a minimum response rate at baseline of 65%, based on rates in other PROFILES studies[40]. During follow-up, after completion of the first questionnaire, we expect a response rate of 80%. The definition of a long total interval will follow from our statistical analysis (see below), however, if the analysis does not provide a clear cut-off point, we will use the last quartile to define the population with a long total interval.

Using the EORTC QLQ-C30, differences of at least 10 points have been considered as clinically meaningful[41]. Based on results from our ongoing PROFILES studies, a standard deviation of about 20 points for each scale can be expected. Using an alpha of 0.05, a power of 0.90, and a long diagnostic interval of 25% in the total group of sarcoma patients, with the expected drop-out, would require 265 patients[42]. In order to make country-to-country comparisons, we aim to include 265 Dutch and 265 English patients in a timeframe of 18 months with a total follow-up of 24 months.

Statistical analysis

Descriptive statistics (means, standard deviation, median, range, frequencies) will be used to quantify diagnostic intervals and describe the study population.

HRQoL at baseline will be calculated according to the EORTC scoring manual[43]. Missing items will be imputed according to these guidelines, after which an available cases analysis will be performed.

The relationship between total interval length and HRQoL at baseline will be investigated by plotting HRQoL against total interval length as a continuous variable. Linear regression will be used to assess their association. The time point providing a significant difference in HRQoL will be used as a cut-off point for further analysis. If this does not provide a clear cut-off point, logistic regression will be used to assess an association between baseline HRQoL and total interval grouped into suitable categories, such as quartiles. The last quartile will then be used to define the population with a long interval.
Apart from statistical significance, we will look at clinically relevant differences in HRQoL scores as determined by Cocks et al[42]. A small effect size will then be considered as an appropriate value for a cut-off point.

A series of univariate logistic regression analyses will be conducted to assess the relationship between total interval length (grouped by the cut-off point as defined by the previous analysis) and independent variables, such as patient, tumour, and healthcare system risk factors. All factors with $p<0.1$ will then be used in multiple logistic regression

analysis (forced entry method) to investigate whether these factors are independently associated with total interval length.

Apart from total interval length, the association of other patient and tumour characteristics (such as self-efficacy, social support, financial difficulties, histology), and HRQoL at baseline will be investigated using univariate logistic regression analysis. Using the forced entry method, multiple logistic regression analysis will then be performed with all factors with $p<0.1$ to assess what factors are independently associated with baseline HRQoL.
Change in HRQoL during the follow-up period of two years and factors associated with changes in HRQoL will be analysed using repeated measures mixed models. This will be compared between patients with a short and long total interval, using repeated measures analysis of variance, controlling for relevant patient and tumour characteristics, and the patient's baseline score. Clinically relevant differences will be assessed using Cocks' method[41, 42].

Other patient-reported outcomes such as QALYs and psychological distress will be analysed in the same way.

Multivariate analyses will be performed to examine associations between total interval length and (1) QALYs, (2) psychological distress, (3) stage at diagnosis, and (4) tumour size. These analyses will be corrected for potential confounders including patient and tumour characteristics and healthcare system.

Both unadjusted and adjusted multivariate Cox proportional hazard regression analyses will be used to examine whether a long total interval is associated with of PFS or OS. PFS is defined as the time interval between diagnosis until clinical or radiological progression, as assessed by the treating consultant. OS is defined as the time from diagnosis until death.

Statistical analyses will be performed using IBM SPSS 25.0; two-sided p-values <0.05 will be considered statistically significant.

Missing data

Online questionnaire completion does not allow for missing data, unless participants have not completed the entire questionnaire, as patients are unable to proceed to the next question until all questions on the current page have been answered. Items missing from paper questionnaires will be dealt with as missing at random. The EORTC-QLQ-C30 allows imputation of missing values according to the EORTC scoring manual guideline[43]. Numbers of missing items will be reported.

Impact of COVID-19 pandemic on QUEST

A national lockdown was introduced across The Netherlands on March 16 and the UK on March 23, 2020, as part of the national strategies to flatten the curve of the COVID-19 pandemic. On March 23 recruitment for QUEST was finished in The Netherlands, while the recruitment target was almost reached in the UK. The COVID-19 pandemic forced us to put the recruitment on hold in the UK. The negative consequences of the pandemic on cancer diagnostic timelines (prolonged), incidence (reduced) and eventually cancer outcomes has been shown and modelled by several studies [44-46]. We will therefor discuss the necessity to reopen recruitment in the UK with our statistical department, as patients recruited during the pandemic will not be representative for the sarcoma population outside COVID times and will bias our results.

Ethics and dissemination

The study was approved by the Health Research Authority and Research Ethics Committee of the United Kingdom (18/WA/0096), and by the medical ethical committee of Radboudumc for The Netherlands (2017-3881). Under Dutch law, approval for observational and questionnaire research by one medical ethical committee is sufficient to implement the study at multiple Dutch centres. The study was registered at clinicaltrials.gov (NCT03441906).

Results from the QUEST study will be published and disseminated via peer-reviewed journals, local, national, and international conferences, and via patient meetings and patient advocates.

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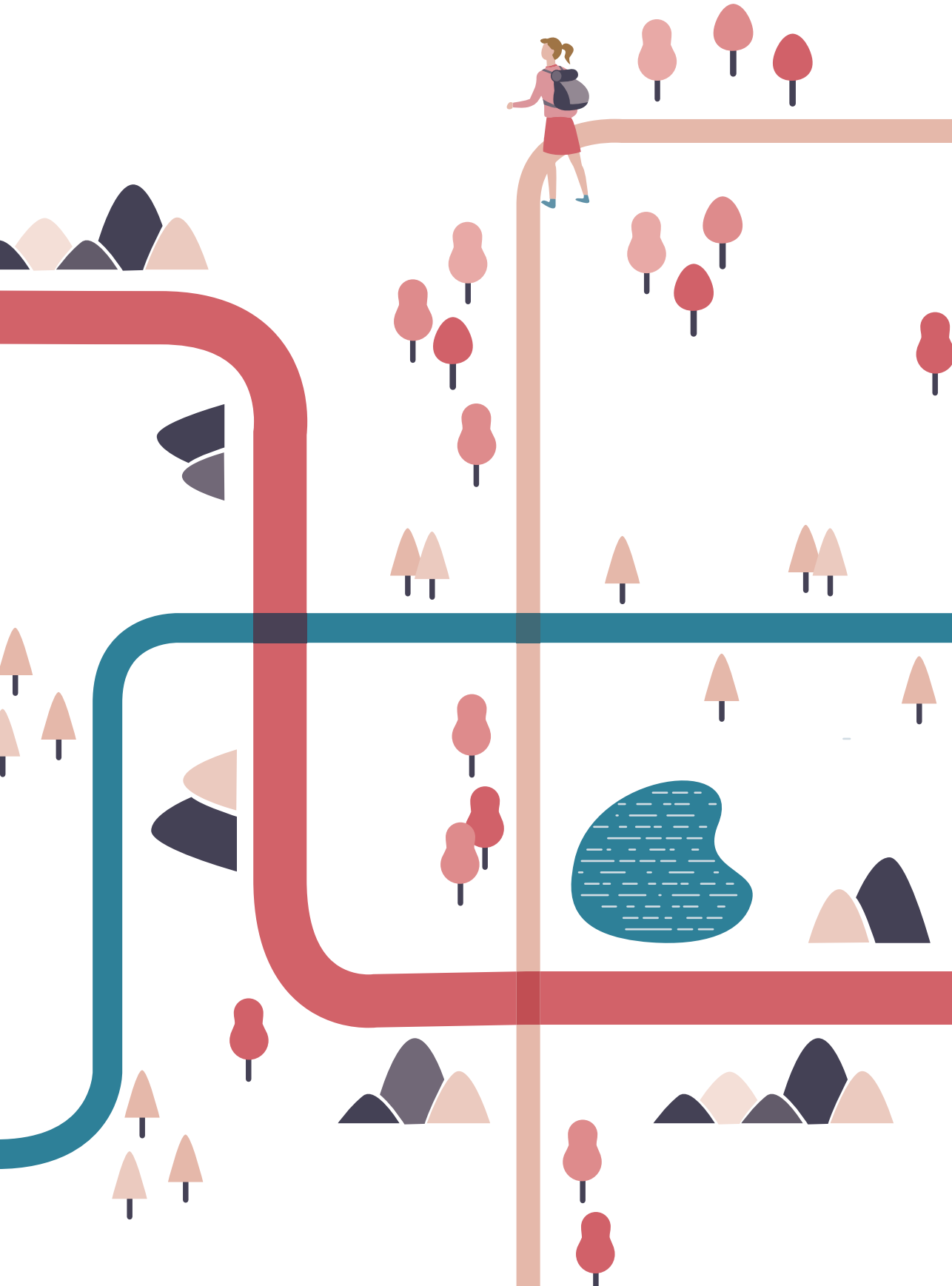

CHAPTER 8

General discussion and future perspectives

One of the pitfalls in diagnosing sarcoma lays in its rarity. Sarcomas are unknown to many patients and healthcare providers, leading to low awareness. This is common for all rare cancers. Sarcomas, however, are heterogeneous with respect to age of onset, site, and biological behaviour, resulting in the absence of a "typical presentation". This increases the chance that both patients and healthcare providers do not recognize its symptoms as a sign of cancer, resulting in prolonged diagnosis and possibly worse outcomes. In this thesis, we aimed to investigate the diagnostic pathway, known as the total interval length, and its effect on clinical and HRQoL outcomes.

We found that total interval length is variable and long in a high proportion of sarcoma patients. Delay can occur in each of its components: the patient interval, as well as the primary, secondary, and tertiary care interval.

In order to optimize the total interval, cut-off points that discriminate between a short or long interval will be helpful to make guidelines more evidence-based, and guide patients and healthcare providers. Currently, guidelines that provide a timeline for diagnosis do so based on expert opinion, and these timelines are not sarcoma specific. In the Netherlands for example, the SONCOS guideline states that the optimal time between referral and diagnosis should be 4 weeks[3]. If a patient is being referred to another hospital, an additional 3 weeks may be added. In England, patients suspected of cancer are referred under the "two-week-wait rule": after referral by a general practitioner, patients get a cancer specialist appointment within two weeks[4]. For children and young adults suspected of bone sarcoma a very urgent referral, meaning an appointment within 48 hours, should be considered. The guideline doesn't provide a timeline for time to diagnosis or treatment after referral to the hospital. However, there is a lack of evidence for the relevance of these specific cut-off points, apart from the fact that psychological stress may decrease if the waiting time from general practitioner to cancer specialist is short. For sarcomas specifically, even after symptoms are recognized as caused by sarcoma, pathological and molecular diagnosis may add an additional 1-2 weeks to establish a final diagnosis. However, getting a specific diagnosis will guard the patient from incorrect treatment strategies. Therefore, cut-off points for complex diagnoses, such as sarcomas should probably differ from other cancers and could differ between histological subtypes.

The relevance of cut-off points is currently based on better overall survival (OS) with shorter diagnostic pathways in some cancers, such as breast, colorectal, head and neck, testicular, and melanoma[5]. For patients with sarcomas, that has never been proven. Historically, evaluation of oncologic care has focused on clinical outcomes, such as treatment-related toxicities and overall survival. Currently, increasing attention is being given to patient-reported outcomes (PROs). HRQoL is an example of a PRO and refers to the impact of disease and treatment on domains of physical, psychological, and social functioning[6].

Apart from a cut-off based on clinical outcomes, HRQoL may be an outcome with clinical relevance to provide guidance for the length of diagnostic trajectories.

The studies discussed in this thesis were not designed to define a cut-off point and were unable to distinguish between a short and a long interval based on outcomes. In all our research we have used the term "interval length", and as long as a clear cut-off point hasn't been identified, researchers should avoid the term "delay". With this thesis, risk factors for longer intervals were identified, and the effect of a longer total interval on health-related quality of life was presented.

Total interval length: contributing factors

To shorten the total interval, it is important to gain insight in factors contributing to a short or long interval respectively. These factors can be divided into patient, tumour, and healthcare system factors.

Patient factors

Our systematic review found bone sarcoma (BS) patients with older age to be at risk for a long total interval. However, the data studied in this review was heterogeneous regarding inclusion criteria and study design and no definite conclusion can be drawn from these results. In soft tissue sarcoma (STS), no associated factors could be identified.

Age was a factor associated with diagnostic interval length in our SURVSARC study: patients aged 18-39 had a higher chance of a long diagnostic interval than those aged ≥40. This trend was also seen in a survey among sarcoma patients in the UK and is a known phenomenon among AYAs in other cancer subtypes[7-9]. Furthermore, when comparing our YA participants aged 25-39 with a TYA cohort aged 12-24, the YAs had longer patient intervals. The difference was significant for YAs diagnosed with STS with a patient interval >3 months, compared to TYAs diagnosed with STS. Patients in the YA age group are at higher risk for a longer total interval compared to both TYAs and older adults. This difference is probably multifactorial and could be related to age-specific events and priorities, and low awareness about the occurrence of malignancies at this age. TYAs may consult a doctor earlier than YA due to interference of parents (although at a later stage than younger children), while patients aged ≥40 may be more aware that symptoms could origin from a cause that does not dissolve by itself have a shorter face of appraisal before they seek help.

Results from the interviews with sarcoma patients showed how diverse diagnostic pathways are, and how difficult it is for both patients and healthcare providers to attribute

symptoms to a sarcoma diagnosis. Factors leading to a long patient or diagnostic interval were not sarcoma specific, e.g. interference with daily life has been known to contribute to a long patient interval in other diagnoses as well, but possibly occur in a higher proportion of patients compared to common cancers. Low awareness among patients and healthcare providers is more specific for rare diseases and cancers occurring at young age but is a difficult factor to improve. This is supported by an English study, in which primary care data of 10953 patients with 28 types of cancer was collected, and patient and primary care intervals were compared[10]. Patients with sarcoma had second longest median pre-referral time (patient and primary care interval combined) with 52 days, only patients with laryngeal cancer had to wait longer before referral (median 58 days).

Interestingly, in our SURVSARC study, no patient factors were identified to contribute to a long patient interval length. This is consistent with other sarcoma and cancer studies, in which no association or conflicting results about the association between patient factors and patient interval length were found[7, 8]. Macleod et al reviewed patient risk factors for delayed presentation for common cancers, using two worldwide systematic reviews of the literature[8]. They report conflicting results, e.g. older age was found to be a risk factor for breast cancer, but not for colorectal, urological, and lung cancer. Younger et al reported age was not related to time to diagnosis among sarcoma patient selected from the National Cancer Patient Experience Surveys in the UK[7]. However, again the primary aim of these studies was not to study the diagnostic pathway.

Gender was found to be associated with diagnostic interval length in the SURVSARC study: female gender was associated with a long diagnostic interval. This is also found in general cancer literature[8, 11], a finding that may be explained by both longer patient intervals: females are found to delay seeking help when detecting potential cancer-related symptoms, as well as longer diagnostic interval: healthcare professionals may overlook symptoms based on patients' gender only as well[12, 13]. Among our YA population, gender was not associated with patient or healthcare interval length.

The identified associated patient factors, or absence thereof, are thus neither specific for the sarcoma population, nor are there any factors specific for the survivorship population. This makes it difficult to formulate recommendations that shorten the total interval based on patient factors.

Tumour factors

Our systematic review did not identify any tumour factors, such as sarcoma subtype, stage at diagnosis etc, associated with interval length; results among included studies were conflicting. Researchers have argued that this lack of an association, known as the 'waiting-time paradox', is caused by the biological phenotype of the tumour, which may

be more important for survival than a short diagnostic interval. Most studies have not been able to adjust for the aggressiveness of the tumour. Furthermore, study designs may not have been optimal to detect these associations: most studies included a small number of sarcoma patients with heterogeneous diagnoses and used retrospective data.

One may hypothesize that low-grade, indolent tumours do not trigger patients to seek help, resulting in a long patient interval. This hypothesis was not only supported by our qualitative data as presented in chapter 3, but was also supported by our SURVSARC study, where patients with a sarcoma located in the skin or pelvis reported a longer patient interval. Sarcomas located in the skin are often indolent, such as dermatofibrosarcoma protuberans, whereas pelvic sarcomas often cause nonspecific symptoms. On the other hand, liposarcomas, rhabdomyosarcomas, and tumours diagnosed at stage III disease, were found to have shorter patient intervals. These tumours often show rapid growth, causing patients to seek help. The survivorship selection of the SURVSARC study may even underestimate the association, as tumours with aggressive biological behaviour are probably underrepresented among our participants. Within our YA study, participants diagnosed with sarcoma showed a trend of being more likely to have a long patient interval than those diagnosed with breast cancer. However, this was not a unique finding; a diagnosis of melanoma and cervical cancer was also associated with a longer patient interval in this study.

Histology was also associated with diagnostic interval length in our SURVSARC and YA study. In the survivorship population, diagnoses of synovial sarcoma and chordoma were associated with a longer interval. This may be caused by the broad differential diagnosis of the complaints these patients present with. Among YAs, patients diagnosed with STS were also more likely to have a longer healthcare interval. Although this association was very strong for sarcomas, it was not specific: participants with lymphoma, melanoma, ovarian cancer, thyroid cancer, colorectal cancer, and cervical cancer experienced longer healthcare intervals as well.

Healthcare system factors

Despite the introduction of guidelines for sarcoma diagnostic pathway in the UK, over the past 30-50 years there has been no improvement of total interval length[14-17]. Guidelines often give advice about location of imaging (e.g. at the local hospital or sarcoma centre), timeliness of referral, centralizing care, and use of multidisciplinary teams.

For both STS and BS, studies have shown that investigations prior to referral to a sarcoma centre result in longer total intervals, due to incorrect interpretation, delays caused by sending the images, re-interpreting them, or performing the investigation again at the sarcoma centre[18, 19]. A French study showed that when assessing sarcoma biopsies in

a pathology expert panel, 40% of diagnoses were changed, often leading to a change in treatment plans[20]. Radiologists and pathologists assessing scans and biopsies may be inexperienced in assessing sarcomas, and struggle to formulate the right diagnosis.

In general, literature has shown that centralizing care at sarcoma centres with a multidisciplinary team improves the diagnostic interval because patients (1) do not lose time at local hospitals; (2) receive appropriate imaging; and (3) get a higher rate of correct pre-operative pathologic diagnosis[18, 21-30]. Improvement of these factors decreases tumour size and stage at diagnosis and improves quality of surgery. Centralizing sarcoma care to specialist centres with expert teams shortens secondary and tertiary care intervals and increases the number of correctly diagnosed and treated patients, hopefully not only contributing to a higher standard of care, but also to outcomes for sarcoma patients.

Diagnostic interval length can also vary between geographic regions, especially in countries where there is a profound difference between regions in the availability of CT-scan equipment and number of hospital beds per inhabitant[31]. These findings were supported by our qualitative study, in which diagnostic interval was, among other reasons, lengthened by an ineffective process of additional investigations and long referral times. Our participants acknowledged centralizing sarcoma care often lead to longer travel distances, resulting in difficulties regarding transport, arrangements at work, and travel expenses, but this did not withhold them to visit a sarcoma centre or lead to longer diagnostic intervals. Specialized care at a sarcoma centre should be available for everyone, the diagnostic pathway could be improved if travel expenses would be covered, for instance by insurance companies.

These results suggest that diagnostic interval length could be shortened by centralization, although no studies with direct comparisons between a country where sarcoma care is formally centralized and one where this is not the case have been performed. However, referral pathways and imaging and pathology processes need to be optimized to result in shortening of diagnostic interval as well. Further research is needed to investigate whether countries with large differences between regions, e.g. in access to medical care, will profit from centralization as well. Furthermore, most research has been done in countries where sarcoma care is publicly financed. In our qualitative study, the English participants thought waiting times would have been shorter if they were privately insured. We were unable to assess this in a quantitative way, but an American study found that self-pay patients has a shorter diagnostic interval than public insurance patients, confirming these results[32].

Effect of total interval length on outcomes

Historically, evaluation of oncologic diagnoses and treatments has focused on clinical outcomes, such as overall survival. For sarcomas, it is unknown whether a shorter total interval will result in improvement of clinical outcomes, as studies have given contradictory results. Apart from the "waiting-time paradox", this may be due to the heterogeneity of the study populations.

More recently, increasing attention has been given to patient-reported outcomes (PROs), which report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else[33], to evaluate treatment efficacy. Measuring PROs has been shown to improve the patient experience of care and induces overall survival benefit in metastatic cancer patients[34]. HRQoL is an example of a widely used PRO.

Data about the influence of total interval length on PROs of sarcoma patients were limited. We investigated the association between total interval length and HRQoL among 1099 sarcoma survivors. In this population, HRQoL, as measured with the EORTC-QLQ-C30, was not related to patient or diagnostic interval length. However, we also investigated the association between perceived impact of diagnostic interval length on HRQoL and found that survivors experiencing a negative impact of diagnostic interval length on their current HRQoL, had lower scores on both global health status and all functioning scales. Diagnostic interval length was long for a larger proportion of patients experiencing a negative impact, than for those experiencing a positive or no impact. Participants experiencing a negative impact also showed the lowest coping abilities.

We concluded that the perceived influence of diagnostic interval on HRQoL is more important to sarcoma survivors than its actual length, and perception is associated with coping abilities. Similar findings were found in other cancer and chronic disease studies. Our qualitative analysis supported the findings; many patients experiencing a negative impact still described psychological distress, more physical abilities, and a worse prognosis due to the diagnostic interval length.

The discrepancy between diagnostic interval length on HRQoL scores and perceived influence on HRQoL, may be more related to coping strategies than the diagnostic interval length. Patients with negative feelings regarding their diagnostic pathway showing maladaptive coping strategies, should be offered support in order to improve their HRQoL.

Research in rare cancers

This thesis investigates the diagnostic pathway of sarcoma patients, which is an example of a rare group of cancers. Performing research among rare cancer patients distinguishes several difficulties. One of the major bottlenecks is the limited number of patients affected each year, whilst a large sample size is needed to draw robust conclusions. In our qualitative study we interviewed a limited number of patients, when interpreting its results this should be considered. However, the study has given us great insight in the diversity of sarcoma diagnostic pathways and laid the groundwork for the design of the QUEST study. For our quantitative studies, the SURVSARC and QUEST, we took several steps to include as many patients as possible. First, for the SURVSARC study, we identified patients via the Dutch Cancer Registry, which registers all patients diagnosed with cancer in The Netherlands. Second, we invited patients from six sarcoma centres, resulting in a high number of eligible patients, representing all Dutch surviving sarcoma patients. Treating physicians were involved in the invitation process, which may have increased the response rate. Third, we tried to make participation as easy as possible by providing the possibility to complete questionnaires online as well as on paper. Fourth, we worked with patients and patient advocacies to make sure our study subject was relevant to them and get extra attention for recruitment of participants. Finally, eligible patients could receive support from both employees of PROFILES as well as from the researcher. With this approach, we were able to include 1099 sarcoma survivors, the largest published study until now.

A second limitation of research in rare cancers may be the inaccuracy of pathologic diagnosis. As mentioned before, many sarcoma diagnoses are changed when re-assessed in an expert panel. We tried to overcome this by recruiting patients diagnosed at sarcoma centres, where expert pathologists and multidisciplinary teams are present. Currently, in the Netherlands 93% of BS patients and 76% of STS patients are discussed with a sarcoma centre[35].

Most literature presented in our systematic review was based on retrospective data and studies with different inclusion criteria. This limitation, often seen in rare cancer research, may be debit to the contradicting results found in these studies as results are both subject to recall and selection bias. This is also the case for our SURVSARC study. However, patient-reported dates regarding cancer diagnosis are often accurate when compared to registry data[36]. A prospective design could contribute to minimize these problems.

Future research should collect prospective data and try to achieve high inclusion numbers by multicentre and international designs. This can only be achieved by collaboration. As shown in this thesis, by combining forces we've recruited a large number of participants.

The SURVSARC included patients from all over The Netherlands. However, research collaborations should not stop at borders. Recruitment among an international patient population will provide reliable results and lead to more valuable conclusions. Regarding the diagnostic pathway, healthcare system factors can best be studied in international designs. In Europe, institutions that are involved in the management of patients with rare cancers form the EURACAN network (https://euracan.ern-net.eu/). Their ambition is to establish guidelines, clinical trials, and to develop research projects with international partners. This network, in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC) and patient advocacy groups, could be the framework for future international collaborations.

Clinical implications and recommendations

This thesis confirms that a long diagnostic interval is highly undesirable and has a negative impact on HRQoL. We have identified several factors and events contributing to total interval length which could be optimized. Further research is needed to prioritize improvement strategies, and to study the relevance of these events within different healthcare systems.

Changes to the diagnostic pathway should focus on improving relevant outcomes for patients, these can be clinical outcomes, as well as patient-reported outcomes. Especially for the latter, patient empowerment is important in future approaches to research. In both The Netherlands and United Kingdom, as well as in many other European countries, there are active patient advocacy groups for patients with sarcoma[37, 38]. Their goals are two-fold: first, they aim to provide information for sarcoma patients and facilitate contact with other patients; second, they want to improve care, research, diagnosis, and treatment for sarcoma patients together with external stakeholders. Including patients in new research strategies will improve designs, focus on relevant topics, and provide clinically relevant outcomes. Furthermore, incorporating advocacy groups in research networks may lead to faster research results, as advocacy groups can use their networks for international designs and to increase response rates. They can also play a role in increasing awareness and communication about research results towards (future) patients.

Future perspectives

The aim of future research on the diagnostic pathway of sarcoma patients should be to study the effect of total interval length on outcomes, to identify risk groups, provide a

clinically relevant timeline for the diagnostic pathway, which could differ among sarcoma subtypes, and prioritize improvement strategies.

Strategies to shorten total interval used among other common cancers, such as screening programs, are not suitable for rare malignancies. Other strategies, such as increasing awareness and improving referral pathways seem more feasible for rare cancers. Awareness among the population is difficult to influence, as future patients are not easily identifiable. Up until now, no sarcoma specific patient characteristics have been identified. Increasing awareness among healthcare providers may contribute faster to shortening the diagnostic pathway. A study which showed lumps larger than 5cm and growing were more often sarcomas than those smaller than five centimetres, resulted in a British national campaign where general practitioners received an awareness pack including golf balls[37, 39]. Although there is no report suggesting faster referrals, this playful campaign and its message shall not be forgotten quickly.

Attention should be paid to patient-reported outcomes, and relevant tools should be designed to be measure these among sarcoma patients. As illustrated in our SURVSARC study, the current HRQoL EORTC-QLQ-C30 scale, may not be able to identify relevant issues caused by a long diagnostic pathway, for sarcoma patients. The measure may be too general, and items specific to tumour site or histological subtype are lacking. A possible solution could be to add questions specific for certain subgroups, which have already been designed by the EORTC for several other malignancies (https://www.eortc.be/itemlibrary/). The EORTC is currently performing a study to design new HRQoL tools specific for sarcoma subtypes (EORTC-1749; NCT04071704).

New studies should ideally be designed in a certain way. First, a prospective setting would be ideal to limit recall bias and selection bias. Second, designs should enable to include large numbers of patients: this can be achieved by using international and multicentre designs, but also by making the threshold for participation as low as possible. Third, patients should be included in research collaborations. Furthermore, changes made to the diagnostic pathway, e.g. new referral strategies, should be evaluated. Both improvement in actual interval length and change in outcomes should be monitored.

For the QUEST study, of which no data have been published yet, we used a multicentre design as well. This study is international, recruiting patients from eight sarcoma centres in total, in order to include a representable number of all histologic subtypes. All newly diagnosed and eligible patients are approached by a member of the research team and receive a phone call to answer additional questions and optimize response. Its design allows for identification of patient, tumour, and healthcare system factors associated with interval length.

Conclusion

Despite new insights gained by the different studies on the diagnostic pathway of sarcoma patients within this thesis, there are still a lot of challenges and unanswered questions that need to be addressed to make clear recommendations for improvement strategies of the diagnostic pathway.

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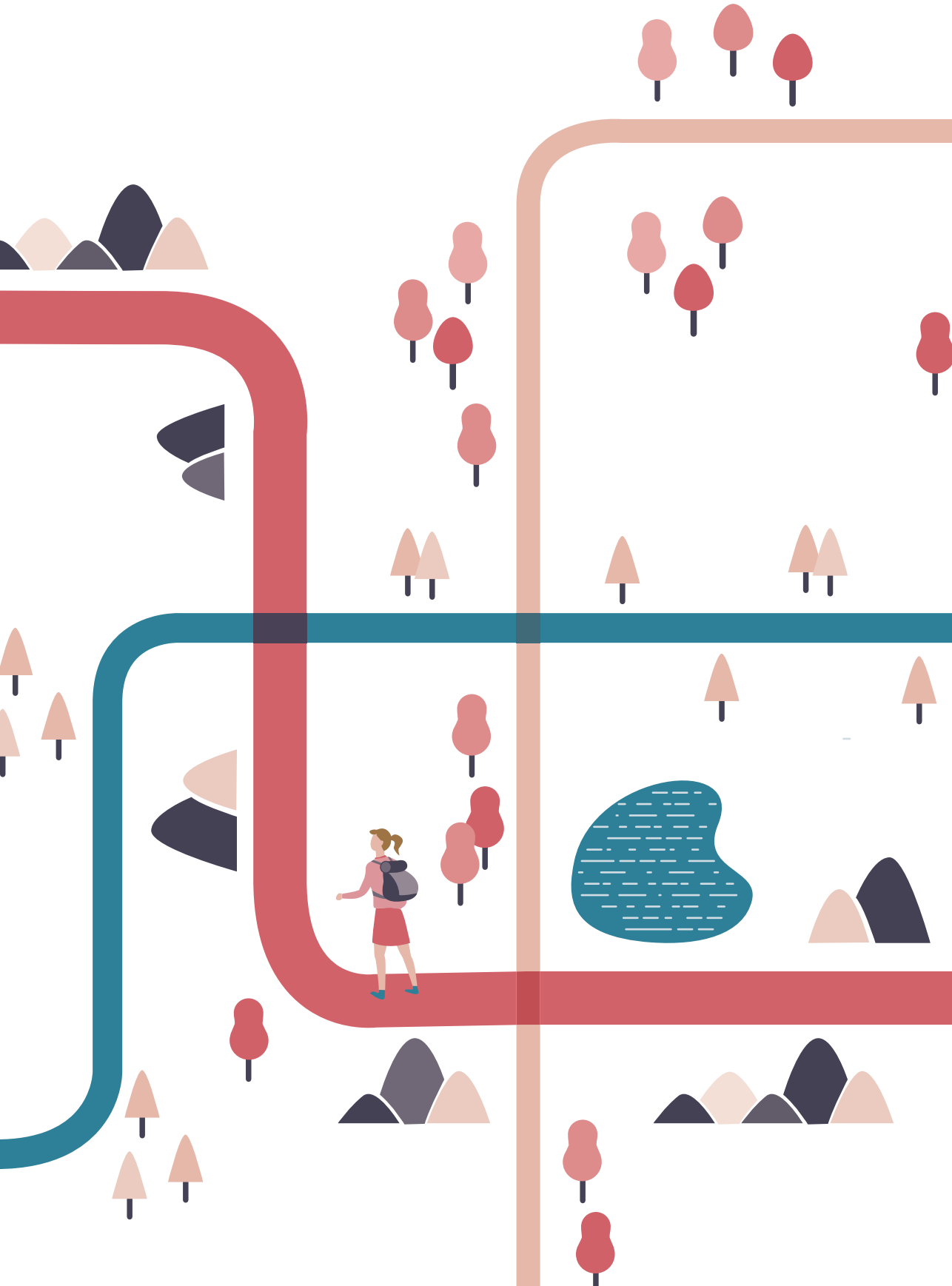
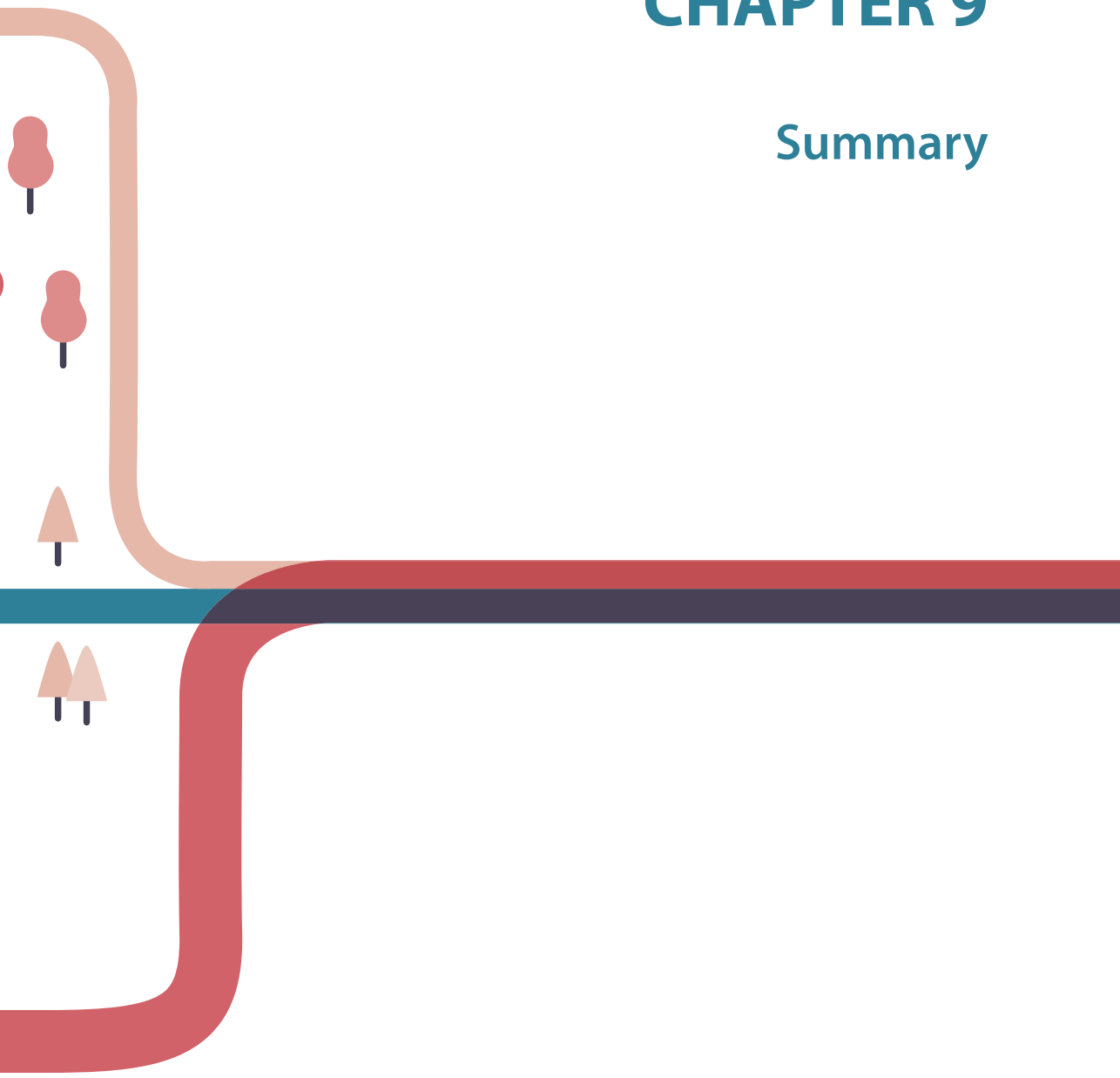




CHAPTER 9

Summary

In this thesis, the diagnostic pathway of sarcoma patients was investigated. This chapter summarizes and discusses the different parts of the thesis. Practical implications and future research perspectives are formulated.

Despite efforts to improve survival outcomes of sarcoma patients with novel imaging and treatment strategies, only limited progress has been made. Another approach to improve survival is to improve the diagnostic pathway. Due to the rarity of the disease and the heterogenous presentation, the diagnostic pathway may be difficult and prolonged, resulting in larger tumours at diagnosis and possibly worse outcomes.

The diagnostic pathway encompasses time from first symptom to histological diagnosis, which is defined as the total interval. This can be divided in a patient interval (time from first symptom until first consultation with a doctor) and diagnostic interval (time from first consultation until diagnosis). The diagnostic interval can be further divided into a primary care, secondary care, and tertiary care interval.

A systematic review was performed in **chapter 2**. The objectives were to quantify total interval length and its components, to identify factors associated with its length, and to determine the impact on patients' outcomes. Both clinical outcomes, such as overall survival, as well as patient-reported outcomes, such as health-related quality of life (HRQoL) were subject of investigation.

Our search resulted in 2310 articles, of which 76 met the inclusion criteria. Total intervals varied broadly; 9-120.4 weeks for bone sarcoma (BS) and 4.3-614.9 weeks for soft tissue sarcoma (STS). Factors associated with a long interval in BS were older age and the lack of performing radiologic examinations upon presentation. In STS, results were conflicting, and no associated factors could be identified.

The influence of total interval length on clinical outcomes remains unclear. One might hypothesize that sarcomas with more aggressive behaviour have a shorter total interval and worse survival outcomes, whilst sarcomas with indolent behaviour have a longer total interval and improved survival. Alternatively, it may be expected that shorter total intervals lead to earlier treatment and better outcomes. Neither of these hypotheses could be supported by our review, as results from individual studies were conflicting. This was possibly the case due to the heterogeneity in design and included sarcoma subtypes. No study examined the impact on HRQoL.

In neither bone or soft tissue sarcoma did we identify a clear cut-off point for appropriate versus inappropriate length of total interval or its components.

In **chapter 3** we investigated the diagnostic pathway in more detail, as experienced by adult sarcoma patients. Fifteen sarcoma patients from the Netherlands and United Kingdom were interviewed, followed by qualitative content analysis. The interviews focussed on the route to diagnosis, factors contributing to total interval length from a patients' perspective, the impact of the route to diagnosis on HRQoL and care satisfaction, and differences in experiences between Dutch and English patients.

Participants had a total interval varying between 10-145 weeks. Both patient and diagnostic interval contributed to total interval length: patient interval ranged from 0-119 weeks, diagnostic interval from 3-140 weeks. Qualitative analysis resulted in four main themes: patient interval, diagnostic interval, reflection on the route to diagnosis, and recommendations for improvement.

The patient interval could be divided into two stages: appraisal and help-seeking. If symptoms were attributed as benign, did not interfere with daily life, or were expected to cease by themselves, appraisal, the time period of assessing symptoms, could last long. The main trigger of help-seeking was interference of symptoms with daily life.

The diagnostic interval was prolonged by six factors: incorrect working diagnosis, ineffective process of additional investigations (e.g. passive waiting time), long referral times, course of disease progression different than expected, long time for histological diagnosis, and lack of lead clinician. English patients perceived their waiting times to be longer than Dutch patients and perceived healthcare providers to be under pressure.

When patients reflected on their route to diagnosis, they commented on subjects related to care satisfaction, impact of receiving the diagnosis, and impact of a perceived diagnostic delay. Long waiting times, false reassurance and inadequate information provision led to dissatisfaction and a high emotional burden.

Factors for improvement of care included increasing awareness of patients and healthcare providers to consider sarcoma diagnosis, empowering patients, and having a lead clinician.

The study confirmed the findings of our review; the diagnostic pathway of sarcoma patients is variable, and its length is influenced by patient and healthcare system factors. Furthermore, the route to diagnosis influences patients' care satisfaction and emotional status. It showed the need for adequately designed quantitative research to confirm its findings. This thesis describes three such studies: the SURVSARC, about the diagnostic pathway among sarcoma survivors; the QUEST, a prospective study among newly diagnosed patients with sarcoma; and a study among young adults, comparing their

diagnostic pathway with patients with other cancer diagnosis, and comparing it with younger patients with cancer. These studies will now be described in more detail.

First, the SURVSARC study. Since no data were available on the diagnostic pathway of sarcoma survivors, we conducted a cross-sectional cohort study among Dutch sarcoma patients, diagnosed 2-10 years prior to the study in one of the six participating sarcoma centres. Participants were selected from the Dutch Cancer Registry. Our efforts resulted in the inclusion of 1099 participants (response rate 58%) who completed one questionnaire on the diagnostic pathway and quality of life. Additional clinical data was extracted from the Dutch Cancer Registry. In **chapter 4**, the first report of this SURVSARC study described the total interval length and its components, and identified factors associated with prolonged intervals.

The patient interval lasted ≥1 month in 60%, and ≥3 months in 36% of participants. Factors associated with a patient interval ≥3 months were sarcoma of skin and pelvis. Liposarcoma, rhabdomyosarcoma, or stage III disease were associated with a shorter patient interval. Diagnostic interval length was ≥1 month in 55%, ≥3 months in 28%. Factors associated with a diagnostic interval ≥3 months were being female, aged <40, or having a synovial sarcoma or chordoma.

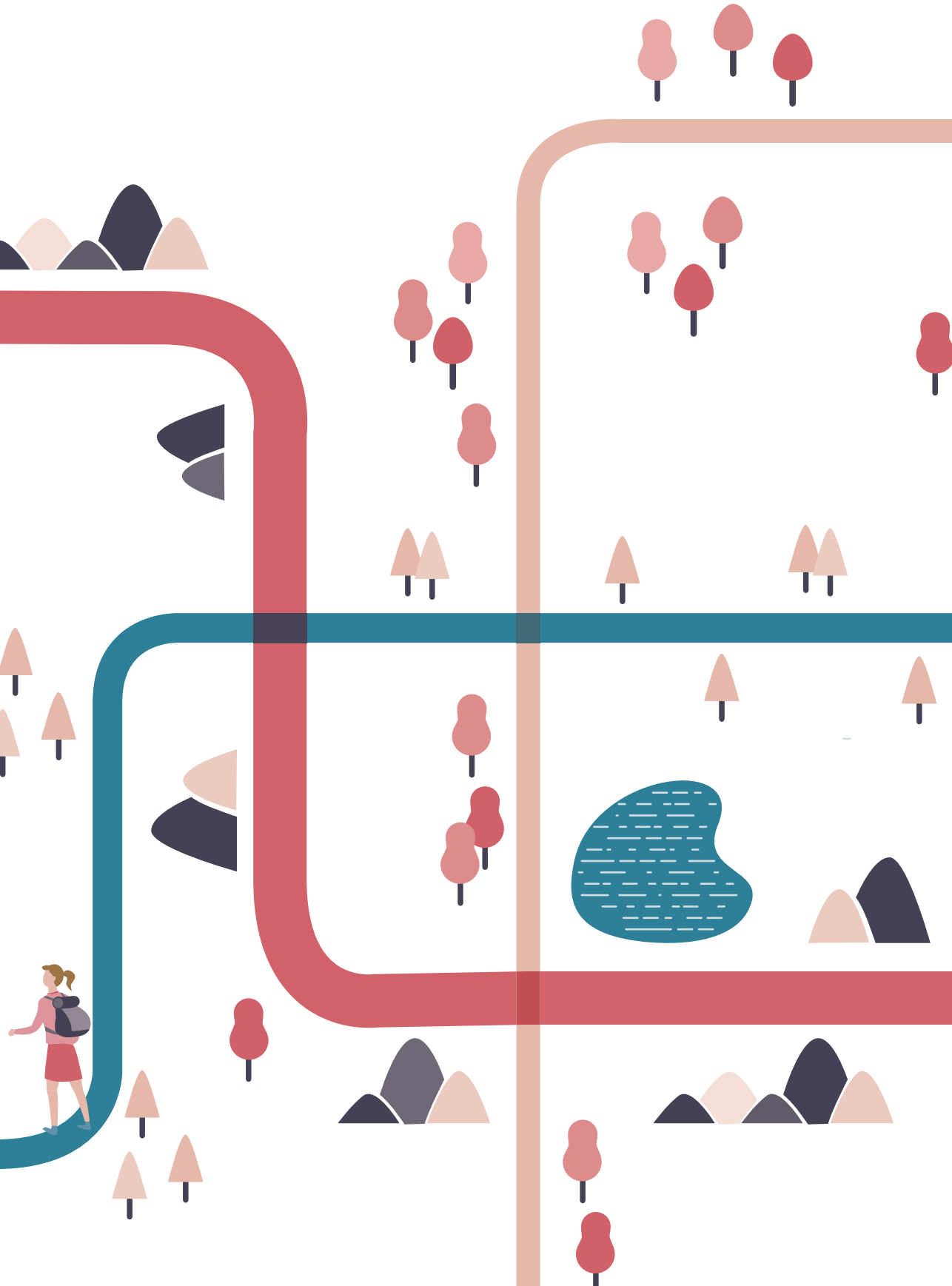
In **chapter 5** we investigated the relationship between time to diagnosis and HRQoL among participants of the SURVSARC study. We showed that HRQoL scores were not influenced by time to diagnosis, but patients' perception of the impact of diagnostic pathway length did influence HRQoL scores. Participants perceiving a negative impact had lower HRQoL scores than those perceiving a positive or no impact, and more often showed maladaptive coping strategies. In addition, we analyzed the answers given in the open text field of the question "Why do you think your diagnostic interval influenced your HRQoL negatively?". The qualitative analyses showed that many participants reported psychological distress, physical disabilities, and worse prognosis due to their diagnostic interval length.

Second, we describe the study among young adults. Many patients diagnosed with sarcoma are adolescents and young adults (AYA), forming a distinct group within the heterogeneous sarcoma population. Unique within this group of patients are their developmental issues and the life events they go through (e.g. becoming financially independent, caring for small children). Furthermore, the distribution of cancers and sarcoma histological subtypes differs from those diagnosed at older age. The characteristics of this specific group of patients may contribute to a prolonged diagnostic pathway. Since decades much attention has gone to researching factors for improvement among teenagers and young adults (TYAs), aged 12-24, but evidence regarding the diagnostic

pathway of young adults aged 25-39 is lacking. We conducted secondary analyses on a cross-sectional study in the United Kingdom about the diagnostic pathway of young adults aged 25-39 at cancer diagnosis in **chapter 6**.

We analyzed data of 341 participants, including 22 sarcoma patients. The patient interval lasted >1 month in 53% of sarcoma patients, and >3months in 42%. When compared to breast cancer (reference group), there was a trend for a longer patient interval for sarcoma patients (OR=2.1 (95%CI 0.9-5.3)). The healthcare interval lasted >1month in 73%, which was significantly longer than for breast cancer patients (OR=14.1 (95%CI 4.9-40.8)). Nearly half of sarcoma patients (46%) had a healthcare interval >3 months. The patient interval was compared to a TYA cohort from the BRIGHTLIGHT study, which is a research program assessing specialist care for TYA with cancer in England[1, 2]. Its cohort is the largest study among TYA patients looking at diagnostic timeliness. The patient interval was >1 month in 32% of TYAs, compared to 53% in YAs. At a cut-off of 3 months, the difference was significant: 4% of TYAs compared to 13% of YAs. Participants identified themes to improve the diagnostic pathway, such as raising awareness, adequate information provision, and reducing passive waiting time. These advices were generally not age-specific and did not differ among sarcoma or rare cancers compared to the entire included YA population.

Third, the design of the QUEST study is described in **chapter 7**. The QUEST study (QUality of life and Experiences of Sarcoma Trajectories) is a longitudinal, prospective, and international study, which aims to quantify total interval, identify factors associated with interval length, and determine the association between total interval and HRQoL, stage and tumour size at diagnosis, progression-free survival, and overall survival. Its prospective design will minimize recall and selection bias, generating reliable results. Its international design enables us to compare healthcare systems and identify healthcare system factors contributing to total interval length. All patients newly diagnosed with sarcoma at one of five Dutch or three English sarcoma centres between 2018-2020 were invited to participate. Participants completed a questionnaire as soon as possible after diagnosis, and were asked to complete four more questionnaires during the follow-up period of two years. Questions include the diagnostic pathway, HRQoL, quality of care, and impact of having a rare disease. Additional clinical data was extracted from electronic patient records. The study has included 311 Dutch patients and 228 English patients. The first results will be available early 2021 and will, hopefully lead to advices on how to improve quality of life and outcomes for patients with sarcoma.



CHAPTER 9

Nederlandse samenvatting

De overleving van patiënten met sarcomen – een zeldzame groep van tumoren uitgaande van bot en steunweefsel – is helaas beperkt. In dit proefschrift onderzoek ik hoe het diagnostische traject van patiënten met sarcomen eruit ziet en of dit aanknopingspunten ter verbetering van overleving en kwaliteit van leven biedt.

Sarcomen

Sarcomen zijn kwaadaardige tumoren die ontstaan in de botten of wekedelen, zoals de spieren of bindweefsel. Zij behoren tot de groep van zeldzame tumoren: ze vormen slechts 1,5% van alle soorten kanker die op volwassen leeftijd voorkomen. In Nederland worden per jaar ongeveer 200 patiënten met kwaadaardige bottumoren en 800 patiënten met kwaadaardige tumoren in de wekedelen gediagnosticeerd. Een huisarts zal tijdens zijn carrière waarschijnlijk slechts één of twee patiënten met een sarcoom in zijn praktijk hebben. Er zijn meer dan 100 verschillende soorten sarcomen geïdentificeerd, die zich stuk voor stuk anders gedragen met betrekking tot de specifieke diagnose, plaats in het lichaam waar zij voorkomen, de leeftijd van de patiënt waarop zij meestal ontstaan, agressiviteit van de tumor en overlevingskansen. Naast bot- en wekedelen sarcomen, krijgen in Nederland jaarlijks 400 patiënten een gastrointestinale stromatumor (GIST). Dit subtype sarcoom maakt geen onderdeel uit van dit proefschrift.

Sarcomen die niet verspreid zijn naar andere plaatsen in het lichaam – dus niet zijn uitgezaaid - worden in principe behandeld met een operatie. Het doel van deze behandeling is genezing. Afhankelijk van de agressiviteit van de tumor is aanvullende behandeling met radiotherapie noodzakelijk. Dat gebeurt toenemend vooraf aan een operatie. Voor sommige subtypes sarcomen maakt ook chemotherapie voor en/of na de operatie onderdeel uit van de primaire behandeling.

Bij wekedelen sarcomen wordt zelden als onderdeel van de primaire behandeling chemotherapie gegeven. De indicatie wordt bepaald door het subtype sarcoom en bij extremiteitssarcomen met een hoog risico op uitzaaiingen, wordt chemotherapie ook overwogen voorafgaand aan de lokale behandeling.

De behandeling van botsarcomen verschilt per subtype. De meest voorkomende subtypes zijn osteosarcomen, Ewing sarcomen en chondrosarcomen. De behandeling van (hooggradige) osteosarcomen bestaat uit een operatie in combinatie met chemotherapie vooraf en na de operatie. Ewing sarcomen worden behandeld met een combinatie van chemotherapie en een lokale behandeling die bestaat uit opereren, vaak in combinatie met bestraling. Als er niet geopereerd kan worden, bestaat de lokale behandeling alleen

uit bestraling. Chondrosarcomen zijn veel minder gevoelig voor chemotherapie; zij worden in het algemeen behandeld met alleen een operatie.

Wanneer er uitzaaiingen zijn van een sarcoom wordt er gekeken of er nog een kans bestaat op genezing. Voor de meeste patiënten bij wie een sarcoom is uitgezaaid zijn de kansen op uiteindelijke overleving van de ziekte echter beperkt en richt de behandeling zich niet meer op genezing, maar op het verlichten van klachten en verlenging van leven. Afhankelijk van de hoeveelheid en plaats van de uitzaaiingen, de klachten die een patiënt hiervan ondervindt en de tijd die er zit tussen de diagnose en het ontstaan van de uitzaaiingen, wordt er gekozen voor een bepaalde behandeling. Dit kan een lokale behandeling zijn, zoals operatie of bestraling, of een systemische behandeling met (veelal) chemotherapie.

De overlevingskansen van patiënten met een sarcoom variëren sterk tussen de verschillende subtypes en het stadium bij diagnose. In het IKNL rapport "sarcomenzorg in Nederland" wordt een overzicht van de epidemiologie, aspecten en uitkomsten van zorg van volwassen patiënten met een sarcoom gegeven die zijn geregistreerd in de Nederlandse Kankerregistratie in de periode 2009-2018. Dit rapport laat zien dat na 5 jaar 81% van patiënten met een laaggradig wekedelen sarcoom nog in leven is, terwijl dit slechts 46% is voor patiënten met een hooggradig wekedelen sarcoom[1]. Bij botsarcomen zijn deze percentages 93% en 60% respectievelijk, waarbij er nog een aanzienlijke variatie per subtype is. Ongeveer 7% van patiënten met een botsarcoom en 14% van patiënten met een wekedelen sarcoom hebben uitzaaiingen bij diagnose, maar ook hierbij is de variatie per subtype heel groot[1]. Bij botsarcomen had 42% van de patiënten met een Ewing sarcoom uitgezaaide ziekte bij diagnose, tegenover 2% bij chordomen. Bij wekedelensarcomen was de kans op uitzaaiing bij diagnose het grootst bij leiomyosarcoom: 25%, en het kleinst bij dermatofibrosarcoom: <1%[1].

Het diagnostisch traject

In het IKNL rapport "Kankerzorg in beeld: zeldzame kanker" uit 2018 wordt benoemd dat het diagnostische traject van zeldzame kankers vaak moeilijker is, langer duurt en leidt tot een slechtere uitgangssituatie[2]. Deze slechtere uitgangssituatie leidt mogelijk tot slechtere overleving of kwaliteit van leven. Doordat sarcomen zeldzaam zijn, op alle leeftijden voorkomen en geen typische klachten of symptomen hebben, is de diagnose sarcoom vaak moeilijk te stellen. Bovendien is er expertise nodig om tot de juiste histologische sarcoom diagnose te komen. Hierdoor is er na huisarts en perifeer specialist vaak nog een doorverwijzing naar een expertisecentrum nodig voor aanvullende diagnostiek.

De tijd tot diagnose wordt gedefinieerd als het tijdsinterval tussen het moment waarop de patiënt voor het eerst een klacht ervaart die veroorzaakt wordt door een sarcoom, tot het moment van definitieve diagnose. Dit tijdsinterval noemen we het totale interval en kan worden onderverdeeld in een patiënt interval en diagnostisch interval. Het patiënt interval is de tijd tussen het ervaren van de eerste klacht en het moment waarop het eerste consult met een (huis)arts plaatsvindt. Het diagnostisch interval is de tijd tussen het eerste consult en het stellen van de diagnose sarcoom. Het diagnostisch interval kan verder worden onderverdeeld in een eerstelijns interval (de tijd dat een patiënt bij de huisarts is voor zijn klachten gerelateerd aan sarcoom), een tweedelijns interval (de tijd dat een patiënt door een medisch specialist in een algemeen ziekenhuis onderzocht wordt voor zijn klachten gerelateerd aan sarcoom) en een derdelijns interval (de tijd dat een patiënt door een medisch specialist in een sarcoom expertisecentrum onderzocht wordt).

Eerdere onderzoeken hebben laten zien dat de tijd tot diagnose heel variabel en lang is bij een groot deel van de patiënten met een sarcoom[3]. De tijd tot diagnose kan variëren van enkele weken tot jaren. Verschillende factoren zouden van invloed kunnen zijn op de duur van het totale interval. Deze kunnen worden onderverdeeld in patiënt factoren (bijvoorbeeld sociodemografische karakteristieken), tumor factoren (zoals histologisch subtype) en zorgsysteem factoren (bijvoorbeeld routes van verwijzing).

Bij sommige vormen van kanker, zoals borstkanker, darmkanker of melanoom, is aangetoond dat een kortere tijd tot diagnose leidt tot een betere prognose[4]. Bij sarcomen is vooral onderzocht of een langere tijd tot diagnose leidt tot een grotere tumor, met een kleinere kans op een complete resectie en groter risico voor het krijgen van uitzaaiingen[5]. Onderzoek naar de relatie tussen tijd tot diagnose en overleving voor patiënten met sarcoom ontbreekt.

Van oudsher zijn artsen vooral geïnteresseerd in klinische uitkomstmaten, zoals overleving. Patiënt gerapporteerde uitkomstmaten zijn nieuwere manieren om artsen en patiënten te informeren. Met behulp van patiënt-gerapporteerde uitkomsten geeft de patiënt zijn of haar mening en waardering over de eigen gezondheid. Kwaliteit van leven is een goed voorbeeld van een patiënt gerapporteerde uitkomstmaat. Kwaliteit van leven zegt iets over hoe de patiënt zijn functioneren ervaart op fysiek, psychisch en sociaal gebied. Tot dusver is er geen onderzoek gepubliceerd waarin gekeken is naar het effect van tijd tot diagnose op de kwaliteit van leven van patiënten met een sarcoom.

Doel van dit proefschrift

Het doel van dit proefschrift is om inzicht te krijgen in het diagnostisch traject van volwassen patiënten met een sarcoom, om risicofactoren van een lange tijd tot diagnose te vinden en het effect van een lange tijd tot diagnose op zowel klinische als patiënt gerapporteerde uitkomstmaten te bestuderen.

De onderzoeken in dit proefschrift zijn uitgevoerd onder Nederlandse en Engelse sarcoompatiënten. In Nederland krijgen jaarlijks ongeveer 1200 en in Engeland 5000 mensen de diagnose sarcoom. Deze twee landen hebben zowel een ander zorgsysteem, als ook verschillen ze in de organisatie van sarcoomzorg. Om deze reden is het mogelijk de invloed van zorgsysteemfactoren op het diagnostisch traject te bestuderen. In beide landen speelt de huisarts een grote rol: in het algemeen is dit de eerste dokter die mensen spreken over hun klachten, en deze bepaalt of een verwijzing naar het ziekenhuis noodzakelijk is. Indien er sprake is van een sarcoom, wordt de patiënt doorverwezen naar een sarcoom expertisecentrum. In Nederland is dit formeel geregeld voor patiënten met een botsarcoom, voor patiënten met een wekedelen sarcoom is dit een advies. In Engeland is zorg voor alle patiënten met een sarcoom formeel gecentraliseerd; in principe worden alle patiënten doorverwezen naar een expertisecentrum.

Hieronder volgt een overzicht van de belangrijkste resultaten van dit proefschrift. Ten slotte volgen aanbevelingen voor toekomstig onderzoek.

Resultaten van onderzoek beschreven in dit proefschrift

Hoofdstuk 2 geeft een overzicht van de huidige literatuur over het totale interval van sarcoompatiënten. Dit systematische literatuuronderzoek beschrijft 76 artikelen, die een zeer gevarieerde lengte van het totale interval laten zien: voor botsarcomen gemiddeld tussen de 9-120 weken en voor wekedelen sarcomen tussen de 4-615 weken. Patiënten met een botsarcoom die ouder zijn of bij wie geen radiologisch onderzoek wordt ingezet door de eerste arts, hebben een groter risico om een langere tijd tot diagnose te hebben. Voor patiënten met wekedelen sarcomen kunnen geen eenduidige resultaten met betrekking tot risicofactoren worden geformuleerd.

Het effect van een langere tijd tot diagnose op klinische uitkomstmaten zoals overleving blijft onduidelijk omdat de studies tegenstrijdige resultaten laten zien. Er was geen enkel onderzoek dat het effect van langere tijd tot diagnose op kwaliteit van leven bekeek. Op basis hiervan kan geen tijdsduur geformuleerd worden die kan gelden als relevant afkappunt voor een kort versus lang interval.

Hoofdstuk 3 beschrijft de tijd tot diagnose zoals die ervaren wordt door volwassen sarcoompatiënten uit Engeland en Nederland. Voor deze studie werden vijftien patiënten geïnterviewd over hun tijd tot diagnose, factoren die ertoe geleid hadden dat ze snel of langzaam hulp van een dokter inschakelden, factoren die in hun ogen hadden bijgedragen tot een snelle of langzame verwijzing en het effect van tijd tot diagnose op hun kwaliteit van leven en tevredenheid over de zorg.

Het totale interval van deze deelnemers varieerde tussen de 10 en 145 weken. Zowel patiënt als diagnostisch interval droegen bij aan de lengte van het totale interval: het patiënt interval wisselde tussen de 0 en 119 weken, het diagnostisch interval tussen de 3 en 140 weken. Analyse van de interviews leverde inzichten op met betrekking tot vier thema's: het patiënt interval, het diagnostisch interval, reflectie op tijd tot diagnose en aanbevelingen ter verbetering van het diagnostisch traject.

Ten eerste het patiënt interval, waarbij onderscheid kan worden gemaakt tussen het proces van beoordeling van de klachten en hulpzoekend gedrag. Op het moment dat een patiënt zijn/haar klachten ervoer als goedaardig, de klachten niet in de weg stonden van zijn dagelijkse bezigheden, of wanneer een persoon verwachtte dat de klachten vanzelf verdwenen, duurde het langer voordat iemand vond dat hulp noodzakelijk was. De belangrijkste aanleiding om hulp te zoeken was wanneer de klachten dagelijkse bezigheden belemmerden.

Ten tweede het diagnostisch interval. Dit was lang door een zestal factoren: (1) het stellen van een verkeerde werkdiagnose, (2) een inefficiënt proces van aanvullende onderzoeken, (3) lange duur van periode van verwijzing(en), (4) ontwikkeling van de klachten anders dan verwacht, (5) een lange tijd tot pathologische diagnose en (6) het gebrek aan een hoofdbehandelaar. Engelse patiënten noemden vaker dan Nederlandse patiënten dat zij lang moesten wachten op onderzoeken en afspraken en dat hun artsen onder grote (tijds) druk stonden.

Het derde thema was reflectie op de tijd tot diagnose. Lange wachttijden, het krijgen van onterechte zekerheid en onjuiste informatie leidden tot ontevredenheid en een grote emotionele last.

Tenslotte benoemden patiënten factoren die het diagnostisch traject zouden kunnen verbeteren, zoals het vergroten van de bekendheid van sarcomen onder patiënten en artsen, het vergroten van de regie door de patiënt en het toekennen van één hoofdbehandelaar.

De resultaten bevestigden de bevindingen die beschreven zijn in het literatuuronderzoek, en legden de basis voor twee vervolgstudies, de SURVSARC en de QUEST. Daarnaast wordt in dit proefschrift een subanalyse van een derde studie onder Engelse jong volwassenen met kanker beschreven.

Hoofdstuk 4 en **hoofdstuk 5** beschrijven resultaten van de Survivorship Sarcoma (SURVSARC) studie. Het primaire doel van deze studie was het in kaart brengen van de kwaliteit van leven van sarcoompatiënten 2-10 jaar na diagnose.

Voor deze studie werden vanuit de Nederlandse Kanker Registratie patiënten geselecteerd die tussen 2008-2016 de diagnose sarcoom kregen en behandeld werden in een van de zes deelnemende sarcoom centra. 1099 (ex-)patiënten vulden eenmalig een uitgebreide vragenlijst in met vragen over hun diagnostisch traject, kwaliteit van leven, symptomen, ervaren kwaliteit van zorg, informatievoorziening en leven met een zeldzame ziekte. Aanvullende klinische informatie werd uit de Nederlandse Kanker Registratie gehaald. Voor dit onderzoek heb ik mij gefocust op de vragen met betrekking tot risicofactoren van een lang diagnostisch traject en gevolgen van de tijd tot diagnose voor de kwaliteit van leven. **Hoofdstuk 4** beschrijft het diagnostisch traject van deze sarcoompatiënten. Uit deze gegevens blijkt dat het patiënt interval bij 60% ≥1 maand duurde, en bij 36% zelfs ≥3 maanden. Patiënten met een sarcoom van de huid of in het bekken bleken langer te wachten voor zij hulp zochten, terwijl patiënten met een liposarcoom, rhabdomyosarcoom of stadium III ziekte eerder hulp zochten. Het diagnostisch interval duurde ≥1 maand bij 55% van de patiënten, en ≥3 maanden bij 28%. Vrouwen en patiënten jonger dan 40 jaar en patiënten met een synoviaal sarcoom of chordoom, hadden vaker een lang diagnostisch interval.

In **hoofdstuk 5** wordt bekeken of de tijd tot diagnose effect had op de kwaliteit van leven van de patiënten die deelnamen aan de SURVSARC studie. Verondersteld werd dat mensen die een langere tijd tot diagnose hadden een slechtere kwaliteit van leven zouden hebben. Enerzijds door het psychische aspect van het lange wachten, anderzijds doordat de kanker mogelijk groter was, met een uitgebreidere behandeling en complicaties hiervan tot gevolg. De tijd tot diagnose bleek echter niet gerelateerd aan de gemeten kwaliteit van leven. Er werd ook gevraagd aan patiënten of zij dachten dat hun huidige kwaliteit van leven beïnvloed werd door de duur van het diagnostisch traject. Deze subjectieve beleving van de duur van het diagnostisch traject bleek wel geassocieerd met hun huidige kwaliteit van leven. Patiënten die vonden dat de tijd tot diagnose hun kwaliteit van leven negatief beïnvloedt, scoorden ook lager op de gemeten kwaliteit van leven schaal. Deze patiënten gebruikten vaker minder goede strategieën om met hun ziekte om te gaan dan de patiënten die geen of een positieve invloed ervoeren. Zij ervoeren bijvoorbeeld meer hulpeloosheid en waren minder geneigd om hulp te

zoeken of een probleem op te lossen. Daarnaast benoemden patiënten die een negatieve invloed van de duur van het diagnostisch traject ervoeren dat zij nog steeds last hadden van psychologische stress, lichamelijke beperkingen, en een slechtere prognose door de lengte van hun diagnostisch interval. Vroegtijdige begeleiding van deze groep patiënten, waarbij aandacht besteed wordt aan het diagnostisch traject en de manier waarop zij met hun ziekte omgaan, kan mogelijk bijdragen tot een verbetering in kwaliteit van leven.

Veel patiënten die een sarcoom krijgen zijn relatief jong en vallen onder de groep adolescenten en jongvolwassenen (15-39 jaar op het moment van eerste kankerdiagnose). Deze groep patiënten onderscheidt zich van oudere volwassenen doordat zij in een andere levensfase zitten, die wordt gekenmerkt door een snel veranderende psychosociale ontwikkeling en levensgebeurtenissen zoals het afronden van een opleiding, het krijgen van een eerste baan, het aangaan van relaties en het zorg dragen voor jonge kinderen. Deze karakteristieken kunnen leiden tot een langere tijd tot diagnose. Er is veel onderzoek gedaan naar het verbeteren van de diagnose voor jonge kinderen en adolescenten tot 24 jaar, maar de groep 25-39 jaar is nauwelijks onderzocht.

Om de kwaliteit van leven te bestuderen van jong volwassenen in de leeftijd van 25-39 jaar met kanker werd een vragenlijst onderzoek gedaan onder Engelse patiënten. Deelnemende patiënten hadden in de afgelopen vijf jaar kanker gekregen en werden behandeld in een van de zes deelnemende ziekenhuizen. In de vragenlijst werden onder andere vragen gesteld over de diagnose, het diagnostisch traject, de kwaliteit van leven en ervaren kwaliteit van zorg. Voor dit onderzoek richtte ik mij op de vragen met betrekking tot het diagnostisch traject. **Hoofdstuk 6** beschrijft het diagnostisch traject van deze 341 patiënten, waarvan er 22 een sarcoom hadden. Het patiënt interval van de 341 respondenten duurde >1 maand in 53%, en >3 maanden in 42% van de gevallen. In vergelijking met de groep borstkanker patiënten hadden de patiënten met een sarcoom een langer patiënt en diagnostisch interval. Het patiënt interval van borstkanker patiënten duurde >1 maand in 34% van de gevallen, terwijl dit 53% was voor sarcoom patiënten. Het diagnostisch interval duurde >1 maand voor 16% van de borstkanker patiënten en voor 73% van de sarcoom patiënten. Het patiënt interval van de gehele groep deelnemers werd ook vergeleken met een groep tieners en adolescenten in de leeftijd van 12-24 jaar. De data van deze tieners kwam uit reeds gepubliceerde data van een ander onderzoek, waarin vergelijkbare vragen werden gesteld[6]. Het patiënt interval bleek langer te zijn voor de jongvolwassenen: 32% van de jongeren had een patiënt interval >1 maand, in vergelijking met 53% van de jongvolwassenen. Bij drie maanden was het verschil 4% versus 13% voor tieners versus jongvolwassenen.

De jongvolwassenen gaven adviezen ter verbetering van het diagnostisch traject op een open antwoord vraag. Deze adviezen werden kwalitatief geanalyseerd en betroffen

het vergroten van de bekendheid van het voorkomen van kanker op deze leeftijd, het aanbieden van goede informatie aan de patiënt en het verminderen van wachttijden. De adviezen die gegeven werden door jongvolwassen patiënten met een zeldzame kanker verschilden niet van die gegeven door patiënten met een vaker voorkomende kankersoort.

De onderzoeksmethode van de derde studie, de QUEST (QUality of life and Experiences of Sarcoma Trajectories) wordt beschreven in **hoofdstuk 7**. Het doel van deze studie is om zo nauwkeurig mogelijk de tijd tot diagnose te bepalen en factoren te vinden die leiden tot een kort of lang diagnostisch traject. Daarnaast heeft de studie tot doel om vast te stellen of er een relatie bestaat tussen tijd tot diagnose en uitkomstmaten zoals kwaliteit van leven, stadium en grootte van de tumor bij diagnose en overleving. Dit is een prospectieve studie waar patiënten uit vijf sarcoomcentra in Nederland en drie sarcoomcentra in Engeland aan deelnemen. Patiënten vullen een vragenlijst in direct na de diagnose, en vervolgens nog vier keer gedurende een periode van twee jaar. De vragenlijst bevat onder andere vragen over het diagnostisch traject, kwaliteit van leven, kwaliteit van zorg en het hebben van een zeldzame ziekte. Aanvullende klinische gegevens, zoals precieze diagnose, worden uit het elektronisch patiëntendossier gehaald. De opzet van deze studie zorgt er enerzijds voor dat patiënt- en tumorkarakteristieken bestudeerd kunnen worden die een risico vormen voor een lang diagnostisch traject. Anderzijds biedt deze studie ook de mogelijkheid om twee zorgsystemen met elkaar te vergelijken en gezondheidszorgsysteem specifieke factoren als ook eventuele culturele verschillen te onderzoeken. De studie heeft het benodigde aantal patiënten inmiddels geïncludeerd (311 Nederlandse en 228 Engelse patiënten).

Toekomstig onderzoek en aanbevelingen

Dit proefschrift heeft geleid tot meer inzicht in het diagnostisch traject van sarcoom patiënten, maar roept tegelijkertijd ook weer nieuwe vragen op. Nieuwe studies zouden een opzet moeten hebben die er zorg voor draagt dat de bias veroorzaakt door selectie (patiënten die al meer dan 2 jaar overleefd hebben zoals in de SURVSARC studie) en herinnering zo klein mogelijk gemaakt wordt. Deze bias kan tegen gegaan worden door een prospectieve opzet en het ontwerpen van grote, internationale studies. De QUEST-studie is een goed voorbeeld van een dergelijke studie. Wij hopen dat de eerste resultaten van deze studie in 2021/2022 gepubliceerd kunnen worden, en dat deze leiden tot concrete adviezen voor het verkorten van het diagnostisch traject of verbeteren van kwaliteit van leven en andere uitkomstmaten. Behulpzaam hierbij zou zijn wanneer de data een klinisch relevante afkapwaarde voor een kort versus lang traject zou opleveren, welke zou

kunnen verschillen per subgroep sarcoom, zodat er gerichte verbeterstrategieën kunnen worden ingezet.

Strategieën voor verbetering die gebuikt worden bij veel voorkomende kankers, zoals screeningprogramma's, zijn niet geschikt voor zeldzame tumoren. Strategieën die zich richten op het vergroten van de bekendheid en het verbeteren van verwijzingen naar expertisecentra lijken meer effect te kunnen hebben voor patiënten met zeldzame kankersoorten, zoals sarcomen.

Voor het meten van patiënt-gerapporteerde uitkomsten, zoals kwaliteit van leven, lijken schalen ontwikkeld voor patiënten met een veel voorkomende kankersoort minder geschikt om de verscheidenheid aan problemen bij sarcoom patiënten op te sporen. Dit kwam ook uit de SURVSARC-studie naar voren. Een mogelijke oplossing kan zijn om locatie-specifieke items toe te voegen aan een bestaande (algemene) vragenlijst, of om bijvoorbeeld locatie-specifieke sarcoomvragenlijsten te ontwikkelen. Een reeds lopende studie van de EORTC is erop gericht om een meetstrategie te ontwikkelen om kwaliteit van leven zo precies mogelijk te meten bij patiënten met een sarcoom.

Conclusie

In dit proefschrift zijn de resultaten van onderzoeken beschreven bij patiënten met een sarcoom, waarvan het doel was om het diagnostisch traject te beschrijven en aanbevelingen te kunnen doen ter verbetering van de tijd tot diagnose. De onderzoeken in dit proefschrift laten zien dat sarcomen een groep vormen waarin veel variatie zit en dit maakt het lastig om te zeggen welke exacte duur van het diagnostisch traject een negatieve invloed heeft op overleving of kwaliteit van leven. Uit de SURVSARC studie blijkt dat patiënt gerapporteerde uitkomsten belangrijk zijn: zelfs jaren na diagnose gaven patiënten aan dat hun kwaliteit van leven negatief beïnvloed werd door de ervaren duur van het diagnostisch traject.

De in dit proefschrift verworven inzichten dragen bij aan vooruitgang van zorg voor patiënten met een sarcoom. Er zijn echter nog veel uitdagingen om de zorg voor deze patiënten te verbeteren. Het is van belang om te bepalen welke patiënten een groot risico hebben op een lange tijd tot diagnose en welke gevolgen dit heeft voor hun overleving en kwaliteit van leven. Waarschijnlijk zal dit verschillen per subtype sarcoom, daarom zijn studies met grote aantallen patiënten noodzakelijk. De resultaten van de prospectieve QUEST studie zullen hier naar verwachting de eerste antwoorden op geven.

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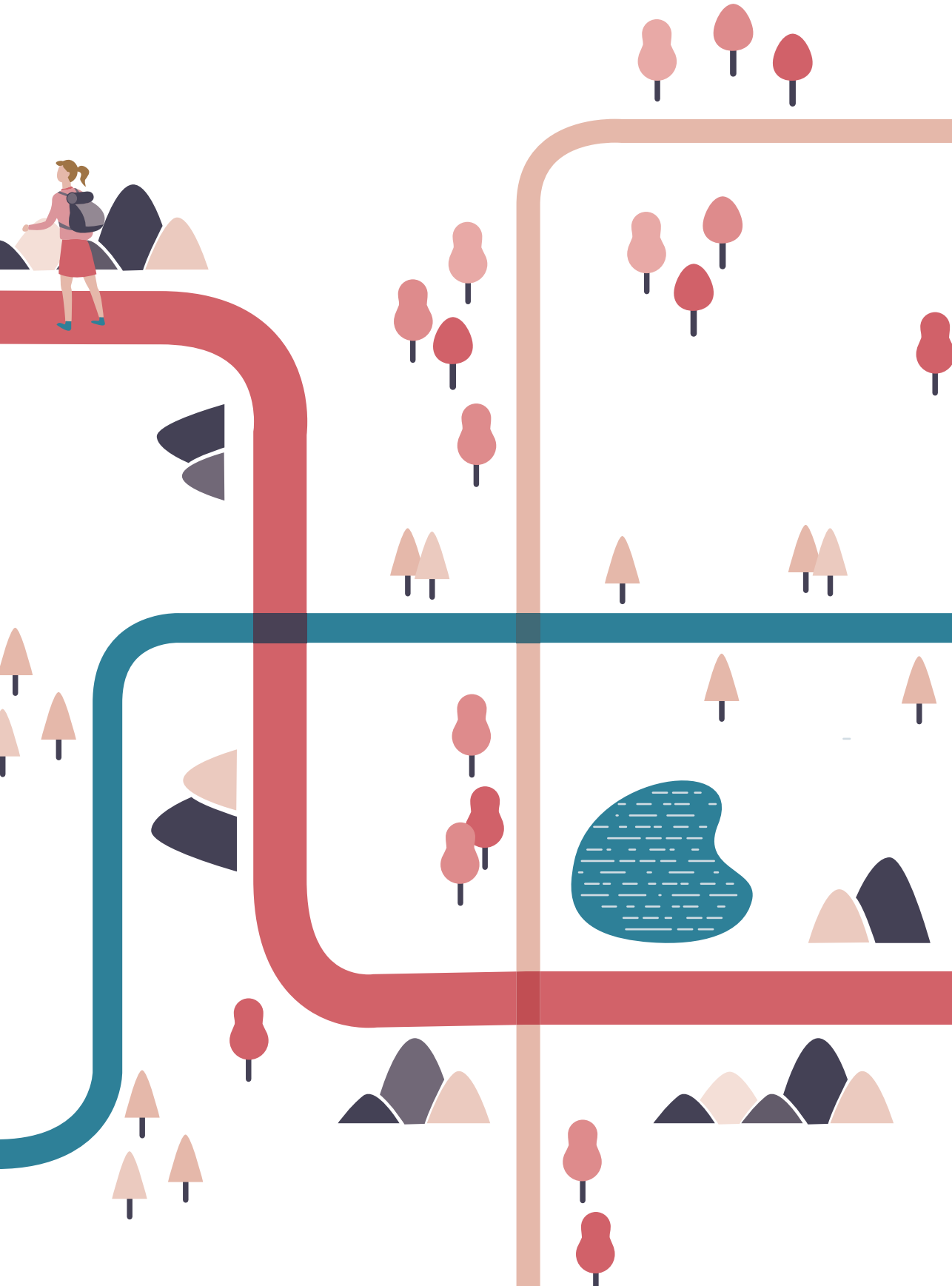

APPENDICES

PhD portfolio

List of publications

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Dankwoord

Institute for Health Sciences
Radboudumc

PhD portfolio

Name PhD candidate: *V.L.M.N. Soomers*	**PhD period:** *01-01-2017 – 30-04-2019 (1.0 fte)* *01-05-2019 – 31-10-2019 (0.2 fte)* *01-11-2019 – 17-5-2020 (1.0 fte)*
Department: *Medical Oncology*	***Promotor(s):*** *Prof. Dr. W.T.A. van der Graaf* *Prof. Dr. L.V. van de Poll-Franse*
Graduate School: *Radboud Institute for Health Sciences*	***Co-promotor(s):*** *Dr. I.M.E. Desar* *Dr. O. Husson*

		Year(s)	ECTS
	TRAINING ACTIVITIES		
a)	***Courses & Workshops***		
-	*Introduction day Radboudumc*	2017	0.5
-	*Graduate School introductory course RIHS*	2017	1.0
-	*BROK course*	2017	2.0
-	*Workshop research professional*	2017	0.2
-	*Course on qualitative analysis*	2017	1.0
-	*E-lectures on focus groups and interviews*	2017	0.3
-	*Biometrics*	2017	4.0
-	*Monthly journal club department of medical oncology*	2017- 2019	3.0
-	*Endnote e-lectures*	2017	0.2
-	*Librarian: how to perform a systematic review*	2017	0.2
-	*Scientific integrity course*	2018	1.0
-	*PhD retreat*	2018	1.0
-	*The art of presenting science*	2018	1.5
-	*Scientific writing skills*	2018	3.0
-	*Science & skills: figure making*	2018	1.75
-	*Radboud talks*	2019	0.4
-	*Academic writing skills*	2019	3.0
-	*SPSS course*	2019	2.0
b)	***Seminars & lectures***		
-	*Rare cancers meetings*	2017-2019	1.0
-	*Weekly multidisciplinary sarcoma meeting*	2017-2018	8.0
-	*Weekly patient discussion department of Medical Oncology*	2017-2019	-
-	*Sarcoma group research meetings*	2017-2019	1.8
-	*Radboud Research Rounds*	2017-2019	0.3
c)	***Symposia & congresses***		
-	*Radboud New Frontiers*	2016, 2018	1.0
-	*Internistendagen*	2017	1.0
-	*Oncologiedagen*	2017, 2019, 2020 2018	1.5
-	*CTOS congress and poster presentation*	2018	1.75
-	*Organizing and giving workshop "wetenschap en opleiding" during MMV congress*	2019	1.0
-	*BSG conference and two poster presentations*	2019	1.5
-	*ESMO conference and poster presentation*	2020	2.0
-	*SPAEN annual conference and ESMO preceptorship sarcoma*		1.5
	TEACHING ACTIVITIES		
d)	***Supervision of internships / other***		
-	*Supervision of Master research thesis Geneeskunde, Miss J. Verhoeven. Subject: HRQoL among sarcoma survivors*	2019	1.0
TOTAL			**49.4**

List of publications

- V.L.M.N. Soomers, I.M.E. Desar, N.P. van Erp, J. Verwiel, S.E.J. Kaal, W.T.A. van der Graaf; Fatal heart failure in a young adult female sarcoma patient treated with pazopanib; Acta Oncol 2017 Sep;56(9):1233-1234. doi: 10.1080/0284186X.2017.1296582.
- V.L.M.N. Soomers, O. Husson, R.J. Young, I.M.E. Desar, W.T.A. van der Graaf; The sarcoma diagnostic interval: a systematic review on length, contributing factors and patient outcomes; ESMO Open. 2020 Feb;5(1):e000592. doi: 10.1136/esmoopen-2019-000592.
- V.L.M.N. Soomers, I.M.E. Desar, L.V. van de Poll-Franse, M.A.J. van de Sande, J.J. de Haan, C. Verhoef, I.J.H. Vriens, W.J. van Houdt, J.J. Bonenkamp, W.T.A. van der Graaf, O. Husson; The Perceived Impact of Length of the Diagnostic Pathway Is Associated with Health-Related Quality of Life of Sarcoma Survivors: Results from the Dutch Nationwide SURVSARC Study ; Cancers (Basel). 2020 Jul 28;12(8):2088. doi: 10.3390/cancers12082088.
- V.L.M.N. Soomers, O. Husson, I.M.E. Desar, M.A.J. van de Sande, J.J. de Haan, C. Verhoef, I.J.H. Vriens, W.J. van Houdt, L.V. van de Poll-Franse, W.T.A. van der Graaf; Patient and diagnostic intervals of sarcoma survivors: results from the SURVSARC study; Cancer, 2020 Dec 15;126(24):5283-5292. doi: 10.1002/cncr.33181
- V.L.M.N. Soomers, I.M.E. Desar, L.V. van de Poll-Franse, O. Husson, W.T.A. van der Graaf; **QU**ality of life and **E**xperiences of **S**arcoma **T**rajectories (the **QUEST** study): protocol for an international observational cohort study on diagnostic pathways of sarcoma patients; BMJ Open 2020;10:e039309. doi: 10.1136/bmjopen-2020-039309
- V.L.M.N. Soomers, W.T.A. van der Graaf, S. Zaidi, SE.J. Kaal, A.J. Hayes, B.H.W.B. Schreuder, R.L. Jones, I.M.E. Desar, O. Husson; The route to diagnosis of sarcoma patients: Results from an interview study in the Netherlands and the United Kingdom; PLoS One. 2020 Dec 7;15(12):e0243439. doi: 10.1371/journal.pone.0243439.
- I. van Eck, D. den Hollander, I.M.E. Desar, V.L.M.N. Soomers, M.A.J. van de Sande, J.J. de Haan, C. Verhoef, I.J.H. Vriens, J.J. Bonenkamp, W.T.A. van der Graaf, W.J. van Houdt, O. Husson; Unravelling the heterogeneity of sarcoma patients' health-related quality of life regarding primary sarcoma location: results from the SURVSARC study; Cancers (Basel). 2020 Oct 22;12(11):3083. doi: 10.3390/cancers12113083.
- C. Drabbe, W.T.A. van der Graaf, B. de Rooij, D.J. Grünhagen, V.L.M.N. Soomers, M.A.J. van de Sande, L.B. Been, K.B.M.I. Keymeulen, I.C.M. van der Geest, W.J. van Houdt, O. Husson; The age-related impact of surviving sarcoma on health-related quality of life: data from the SURVSARC study; ESMO Open. 2021 Feb;6(1):100047 . doi: 10.1016/j.esmoop.2021.100047.
- C. Drabbe, D.J. Grünhagen, W.J. Van Houdt, P.M. Braam, V.L.M.N. Soomers, J.A. Van der Hage, J.J. De Haan, K.B.M.I. Keymeulen, O. Husson, W.T.A. Van der Graaf; Diagnosed with a Rare Cancer: Experiences of Adult Sarcoma Survivors with the Healthcare System - Results from the SURVSARC study.; Cancers (Basel). 2021 Feb 8;13(4):679. doi: 10.3390/cancers13040679.

- V.L.M.N. Soomers, E. Lidington, B. Sirohi, M.A. Gonzalez, A.S. Darlington, W.T.A. van der Graaf, O. Husson; The prolonged diagnostic pathway of young adults (aged 25-39) with cancer in the United Kingdom: results from the Young Adult Cancer Patient Journey Study; *Submitted*

Curriculum vitae

Vicky Soomers werd geboren op 17 mei 1988 in Kerkrade. In 2005 voltooide zij de middelbare school aan het Eijkhagen college te Landgraaf (tweetalig VWO, cum laude) en in datzelfde jaar begon zij aan de studie geneeskunde aan de Radboud Universiteit te Nijmegen. Zij behaalde in 2012 haar artsexamen en kreeg direct een opleidingsplaats Interne geneeskunde in het Radboudumc, onder hoofdopleider prof. Dr. Jos van der Meer, en later prof. Dr. Jacqueline de Graaf en Dr. Gerald Vervoort.

Van 2012-2015 werkte zij in het TweeSteden Ziekenhuis te Tilburg (thans Elisabeth-TweeSteden Ziekenhuis) met als opleider Dr. Thomas Wierema, waar haar interesse in wetenschappelijk onderzoek werd gewekt. In 2014 besprak zij de mogelijkheden hiertoe binnen de afdeling Medische Oncologie van het Radboudumc met Prof. Dr. Winette van der Graaf.

In 2015 zette zij haar opleiding voort in het Radboudumc, alwaar zij in 2016 begon met de differentiatie Medische Oncologie met als opleiders Prof. Dr. Koos van der Hoeven en Dr. Ingrid Desar. Met een subsidie voor een junioronderzoeker die door het Radboud Institute for Health Sciences was toegekend betreffende 'The impact of the diagnostic trajectory in sarcoma patients on stage at diagnosis, primary treatment, clinical outcome and quality of life' kon zij in 2017 haar promotie-onderzoek starten onder leiding van Prof. Dr. Winette van der Graaf, Prof. Dr. Lonneke van de Poll-Franse, Dr. Ingrid Desar en Dr. Olga Husson. Tussen mei en november 2019 werd het promotie-onderzoek part-time voortgezet, en verrichte zij tevens stageonderdelen van de opleiding tot internist-oncoloog. Sinds medio mei 2020 richt zij zich weer op haar opleiding tot internist-oncoloog, welke ze in augustus 2021 hoopt af te ronden.

Vicky is getrouwd met Joep van Dijk. Samen hebben zij een zoon (Arthur, 2020). Joep heeft twee dochters (Meike, 2012; Jasmijn, 2014).

Research data management

The data obtained during my PhD at the Radboud university medical center (Radboudumc) have been captured and stored via the PROFILES database (www.profilesregistry.nl). Coded data was additionally backed-up on university servers in "Statistical Package for the Social Sciences" (SPSS) files. These files did not contain information regarding the identity of the patient (such as name or social security number), and only contained coded-anonymous data.

Data were stored on both my digital personal Radboud workplace environment and a communal Radboud drive. Only researchers within the study team have access to this drive. In this manner, the data can be used for future research.

Transcribed interviews used in my qualitative study were stored on servers of the Radboudumc in "Atlas.ti" files. These were password protected and do not contain information regarding the identity of the patient.

The medical and ethical review board committee of the Radboudumc in the Netherlands or The Research Ethics Committee in the United Kingdom have given approval to conduct the studies within this thesis in which patients were involved. All studies comply with the standards of the Declaration of Helsinki.

Dankwoord

Dit proefschrift was nooit tot stand gekomen zonder de inzet van vele anderen, die ik hiervoor graag zou willen bedanken. Allereerst wil ik alle patiënten bedanken die hebben deelgenomen aan de studies in dit proefschrift. Door hun deelname in een moeilijke periode in hun leven, zijn wij in staat om de zorg voor sarcoompatiënten te verbeteren. Daarnaast ben ik veel dank verschuldigd aan mijn promotieteam.

Prof. Dr. van der Graaf, beste Winette, bedankt dat je me de mogelijkheid gegeven hebt om mijzelf op wetenschappelijk gebied verder te ontwikkelen. Je legt de lat hoog, dat heeft mij altijd gestimuleerd om het goed te willen doen. Ik heb veel geleerd van je kennis en ervaring, en je netwerk heeft voor mij vele deuren geopend. De inkijk in het Engelse zorgstelsel heeft mijn blik verder verbreed en daar zal ik de rest van mijn carrière gebruik van maken. Daarnaast was er ruimte om andere dingen met je te delen. Dank daarvoor!

Prof. Dr. van de Poll-Franse, beste Lonneke, jouw kennis over met name de methodologie heeft de kwaliteit van onze studies enorm geholpen. Ondanks ons laagfrequente contact had jij altijd oog voor de dingen die buiten het promotieonderzoek speelden. Bedankt voor de prettige samenwerking!

Dr. Desar, beste Ingrid, na onze kennismaking in 2014 werd mij duidelijk dat een promotieonderzoek kunnen doen niet vanzelfsprekend was. Toen ik in 2016 startte met mijn differentiatie was dit nog steeds onzeker. Dank voor je inzet om mij dit promotieonderzoek te kunnen laten combineren met de opleiding tot internist-oncoloog. De afgelopen jaren hebben we intensief samengewerkt en is mij gebleken dat ik op veel vlakken op je lijk. Ik waardeer je kritische blik, directe communicatie en kennis enorm. Je gaf (en geeft als opleider nog steeds!) mij kaders, maar laat me daarbinnen mijn eigen keuzes maken. Dank voor je begeleiding en inzet om van mij een betere arts(-onderzoeker) te maken!

Dr Husson, beste Olga, het begon op een koude maar zonnige dag in het AvL, voerde ons vele malen langs Londen en Nijmegen, en een enkele keer naar Strijbeek, Rome, Barcelona, Milaan en Birmingham. Mijn promotietijd eindigt op zomerse dagen achter mijn computer op zolder, met jou aan de telefoon aan de eettafel in Strijbeek. Zonder jouw gastvrijheid, lach, en wekelijks contact waren de afgelopen jaren een stuk saaier geweest. Je wist mij niet alleen wegwijs te maken in het Britse zorgsysteem en de Londense metro, zonder jouw kennis en daadkracht was dit proefschrift nu niet afgerond. Je 'pure' kijk op statistiek en mogelijkheid om dit samen te koppelen aan de kliniek heeft de kwaliteit van de studies en publicaties bepaald. Ik hoop dat er nog veel wijntjes volgen op terrassen of – wie zal het zeggen – in de KLM lounge!

De leden van de manuscriptcommissie, **professor Verheij, professor Merkx en professor Muris,** wil ik hartelijk danken voor het beoordelen van dit proefschrift.

Alle co-auteurs en leden van de sarcoomketens van alle deelnemende centra wil ik bedanken voor de bijdrage aan deze studies, van opzet en inclusie, tot toevoegingen aan de manuscripten. Zonder jullie vertrouwen in mij en onze samenwerking zou gedegen sarcoomonderzoek onmogelijk geweest zijn.

Dank aan de collega's van **IKNL** en **profielstudies** voor jullie ondersteuning bij de uitvoering van de studies in dit proefschrift. Sommigen van jullie zetten je nog steeds in voor de QUEST, dank daarvoor!

A special thanks to our British team members! **Eugenie,** thank you for the work you've put in the QUEST UK study the past year! **Emma,** thanks for sharing the YA database with me, your practical help, and Christmas drinks! **Helena,** thanks for your stories and help with running the QUEST and doing the data management. **Dr. Robin Jones and staff of the sarcoma unit,** thank you for welcoming me to the Royal Marsden and providing me with an insight in sarcoma care in London. Doing research in two countries gave me experiences valuable for the rest of my career.

Prof. Dr. Burger, beste David, als mentor heb ik je gelukkig niet vaak nodig gehad. Bedankt voor je beschikbaarheid en adviezen de afgelopen jaren.

Er zijn een aantal mensen die een belangrijke bijdrage geleverd hebben en mij gemotiveerd hebben om de stap te nemen om promotieonderzoek te gaan doen. Een paar van hen wil ik persoonlijk bedanken. **Dr. Wierema, beste Thomas,** jij was het die vond dat ik toe was aan wetenschappelijke verrijking en mij stimuleerde tot dat eerste gesprek in het Radboudumc. Bedankt dat je mij destijds gestimuleerd hebt! **Dr. Faes, beste Miriam,** als enige gepromoveerde collega-aios in Tilburg enthousiasmeerde jij mij ook om deze kans te grijpen. Jij bent voor mij een voorbeeld als mens, dokter, en moeder.

Beste collega's uit de **dungeon; Minke, Eline, Martine, Wim, Maarten, Mark, Karin, Wouter, Sarah, Janneke, Annelieke, Dide, Gerben, Kim, Maike, Marije, Sandra, Sophie, Lotte, Jorien en Iris**, wat fijn om voor alles bij jullie binnen te mogen lopen. **Beste Minke,** mijn all-time roomie, bedankt voor alle theetjes, wandelingen, verjaardagslunches en het helpen vullen van de enveloppen!

Mijn opleiders, **Prof. Dr. Jacqueline de Graaf, Prof. Dr. Jan Smit, Dr. Gerald Vervoort, Prof. Dr. Ir. Koos van der Hoeven, Dr. Ingrid Desar, Prof. Dr. Carla van Herpen,**

Dr. Anja Timmer-Bonte, bedankt dat jullie mij in staat gesteld hebben om mijn opleiding tot internist te combineren met mijn promotieonderzoek.

Dank aan alle collega's van de afdeling medische oncologie voor de fijne werksfeer de afgelopen jaren, in het bijzonder mijn mede (oud-)fellows die ook dit bijzondere pandemie-jaar zorgen voor persoonlijk contact.

Mijn lieve vriendinnen en jullie partners, jullie geven kleur aan mijn leven! **Sanne, Josanne, Laura, Simone, Rebecca, Lianne, Anne, Iris, Ingrid, Carlijn,** met elk van jullie heb ik een bijzondere vriendschap die mij heel dierbaar is. Ondanks vaak hetzelfde antwoord bleven jullie mij vragen hoe het ervoor stond met mijn promotieonderzoek. Het is af!

Mijn paranimfen. **Sanne**, onze vriendschap hoeft niet in woorden uitgedrukt te worden. Dank dat jij al meer dan 20 jaar aan mijn zijde staat en nooit meer dan één telefoontje ver weg bent. **Rebecca**, mijn partner in crime. Onze sparringmomenten en de spiegel die jij mij voorhoudt zijn onbetaalbaar.

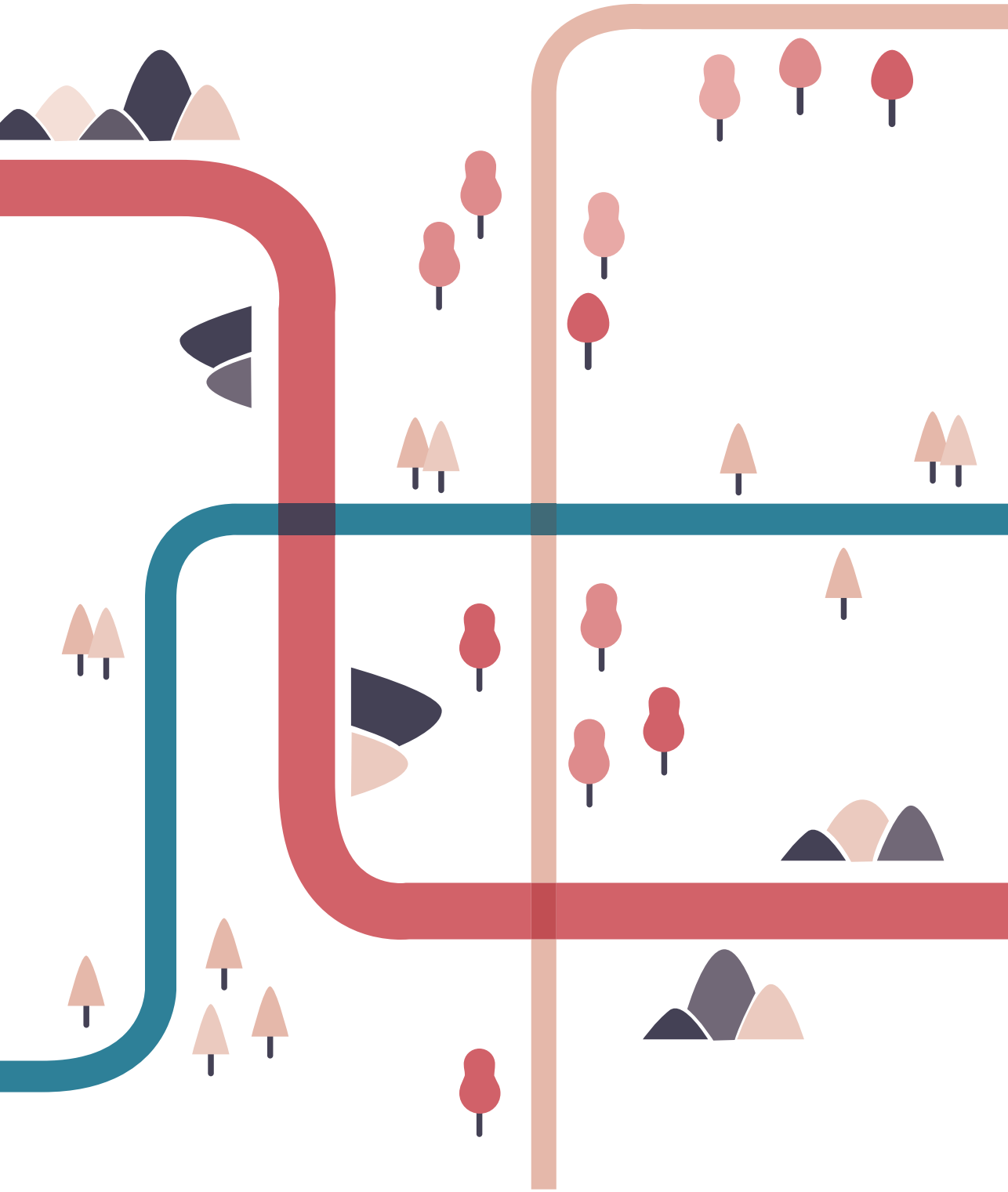
De letter D, mijn schoonfamilie, Kees en Thea, Lieneke en Bart, Bram en Tessa, Marlijn, jullie leerden mij kennen toen ik net gestart was met mijn promotieonderzoek, en hoewel het soms misschien moeilijk te volgen was waar ik nou eigenlijk mee bezig was, bleven jullie informeren hoe het ervoor stond. Lieve Kees en Thea, bedankt dat jullie mij op deze manier in jullie gezin hebben opgenomen!

Mijn familie, waarin flink gediscussieerd kan worden maar we altijd het beste met elkaar voor hebben. Lieve **Luc, Alette, Melissa en Guido,** bedankt dat jullie er altijd voor mij zijn! Lieve **papa en mama,** jullie hebben mij altijd gestimuleerd om te doen wat ik leuk vond, en daarin het beste naar boven te halen. Al kon ik zo slecht leren dat ik wel internist moest worden ☺, jullie hebben mij altijd gesteund. Ik hou van jullie!

Meike en Jasmijn, een onverwachte toevoeging aan mijn leven. Jullie zijn twee slimme en bijdehante tantes, het is genieten om jullie bezig te zien met een knutselwerk of jullie broertje.

Lieve **Arthur,** ik kan nu zeggen: een proefschrift afronden is niets vergeleken met een bevalling. Wat houd ik veel van jou!

Lieve **Joep,** in korte tijd hebben we al veel beleefd! De naam 'QUEST' is aan jou te danken. Bedankt voor het luisteren naar mijn gemopper en het geven van je (on)gevraagde advies. Laten we nog veel beleven samen! Ik hou van jou!



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